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Institute *for* Risk Assessment Sciences

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An inventory, evaluation and way forward to assess the potential socio-economic impact of EDC-associated health effects in the EU

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Final report d.d. April 11, 2016

Colofon

http://www.uu.nl/IRAS

ISBN: 978-90-393-6538-0

This report is commissioned by the Dutch Ministry of Infrastructure and the Environment (IenM). On request of the Ministry of IenM, the report has been prepared under guidance of Julia Verhoeven, MSc and Dr. Betty Hakkert of the National Institute for Public Health and the Environment (RIVM).

The views expressed in this publication reflect the views of the authors (IR, MvD, MvdB). RIVM is not responsible for the content of this report.

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Publiekssamenvatting

Er is steeds meer aandacht voor mogelijke gezondheidsschadelijke effecten door hormoonverstorende stoffen. Dit rapport geeft een overzicht van ziektebeelden die in bestaande literatuur in verband worden gebracht met blootstelling aan hormoonverstorende stoffen. Het resultaat is een overzicht van meer dan 80 ziekten verdeeld over 6 categorieën. De auteurs hebben de bewijslast rondom de link tussen ziekten en hormoonverstorende stoffen niet geëvalueerd. Wel wordt geconstateerd dat dit een punt is van intensieve discussie. Vervolgens zijn eerder verschenen studies vergeleken waarin de mogelijke kosten zijn berekend van ziekten door hormoonverstorende stoffen. Ondanks verschillende benaderingen van deze studies, komen de kostenschattingen redelijk goed overeen. Daarnaast zijn er aanvullende kosten voor 3 ziektebeelden in kaart gebracht, te weten endometriose, neuraalbuisdefecten en astma. In totaal zijn kostenschattingen voor 16 van de ruim 80 ziektebeelden meegenomen. **De totale schatting is dat blootstelling aan hormoonverstorende stoffen mogelijk resulteert in zo'n 46-288 miljard € per jaar aan ziektekosten in Europa (EU28).** Er zijn echter veel onzekerheden rondom deze schatting, met name op het gebied van causaliteit en berekening van kosten. In de ziektekostenschattingen zijn naast directe zorgkosten (bv. behandelingen en medicijnen) ook indirecte kosten meegenomen (zoals productiviteitsverlies) en voor sommige ziektebeelden immateriële schade (bv. verloren levensjaren). De kostenschatting bestaat daarmee slechts voor een deel uit werkelijke kosten die gemaakt worden door de maatschappij. De auteurs concluderen dat het belangrijk is een goed inzicht te krijgen in ziektekostenopbouw om een vollediger inzicht te krijgen in de ziektekosten die mogelijk worden veroorzaakt door hormoonverstorende stoffen. Hiervoor stellen ze een modulaire aanpak voor waarmee kosten voor ontbrekende ziektebeelden kunnen worden aangevuld. In dit rapport wordt deze modulaire aanpak voor een vijftal ziektebeelden geïllustreerd.

Dit rapport laat zien dat de ziektekosten in Europa door hormoonverstorende stoffen mogelijk aanzienlijk kunnen zijn. Een beter inzicht in deze kosten, zoals hier is gegeven, kan helpen bij het prioriteren van beleidsmaatregelen en verder onderzoek naar hormoonverstorende stoffen.

Executive summary

This report aims to provide an improved understanding on the potential socio-economic cost of EDC-associated health effects. Gaps between the required and available information of adequate quality that is relevant for health impact analysis and modelling of socio-economic cost in relation to EDCs, are addressed. The available information from the scientific literature on EDC-related health endpoints and existing modelled costs are summarized, compared and evaluated. Uncertainties that are associated with the causal link between health effects and EDCs are not a focus of the present report. A modular approach is introduced that can provide a method to include additional calculations of potential socio-economic cost and be used to add relevant information on EDC-related diseases. This approach is illustrated for five potentially EDC-related health effects. According to currently available literature, the socio-economic burden of EDC-associated health effects for the EU may be substantial, ranging between € 46 – 288 billion per year. In view of the uncertainties with respect to causality with EDCs and corresponding health-related costs, these estimates should be interpreted with care. Nevertheless, this study indicates that exposure to EDCs may lead to substantial societal costs. The outcome of this literature study warrants further substantiation of the suggested associations as well as health costs for potential EDC-related diseases.

Background

The endocrine system regulates and drives growth, development, homeostasis and reproduction. There is now substantial toxicological evidence that certain chemicals have the ability to interfere with and modulate the endocrine system. In addition, there is evidence that changes in the endocrine system may lead to adverse health effects. Well-known examples of chemicals that are associated with endocrine disruption (so-called Endocrine Disrupting Chemicals or EDCs) include polybrominated diphenylethers (PBDEs), organophosphorus pesticides (OPs), phthalates, bisphenol-A (BPA) and their analogues, as well as the "older" persistent organic pollutants (POPs) such as dichloordifenyltrichloorethaan (DDT), chlorinated dioxins and polychlorinated biphenyls (PCBs). Exposure to many of these chemicals is still ubiquitous. Exposure to EDCs in humans has been associated to a spectrum of diseases and deficits, including metabolic diseases, certain hormone-dependent tumors, neurobehavioral deficits and male reproductive deficits. Also, epidemiological studies indicate that these adverse health effects have increased over the last decades in humans and wildlife (Kortenkamp et al., 2012, UNEP/WHO, 2013, Gore et al., 2015).

The impact of (potential) EDCs on human health and the environment is an area of extensive debate and includes discussion on the definition of an "endocrine disruptor", the criteria to identify chemicals as an EDC, types of related health effect, weight of evidence, mechanisms, methodology for risk assessment and regulatory approach. Over the years, this debate has become more and more polarized, which has slowed down regulatory action on (potential) EDCs in the EU. The observed increase in incidence of endocrine-related diseases together with the yearly high production of industrial chemicals (source: Eurostat) that may exhibit endocrine disrupting effects signify the need for risk managers and regulators to be well-informed on the consequences of the (lack of) regulatory actions with respect to EDCs. **The overall goal of this report is to improve understanding on the extent of potential EDC-related health effects and related socio-economic cost in Europe.**

Inventory of EDC-associated health effects

The past years, the EU, WHO, UNEP and other institutions and groups of scientist have published leading reviews on EDCs that include overviews of (potential) EDC-related diseases, disorders and conditions. These studies used different criteria to determine weight of evidence and/or causality to establish a role for EDCs in specific health effects. Therefore, some differences exist in listed health effects. In this report, an as much as possible complete and clear overview of EDC-associated health endpoints was compiled using these authoritative reviews on EDCs and their effects. This has resulted in a table with over 80 health effects that are associated with EDCs in the literature (Table 1 in the report). These endpoints can be clustered into six major categories: reproductive health, hormonal cancers, neurodevelopmental syndromes and conditions, effects on the metabolic system, immune system disorders and one mixed group of "other" health endpoints. In order to retain the possibility to compare studies, we used as much as possible the definitions of health effects as defined in the reviews used. There is considerable agreement on the categories of health effects that are associated to endocrine disruption. Most consistency among reviews seems to exist within the group of reproductive health effects and group of hormonal cancers. Listing of specific health effects is less consistent in the group of immune system disorders and the group of "other" disorders and conditions.

Causality between EDCs and health effects has been addressed in the scientific studies that are underlying this report. It should specifically be mentioned that we did not evaluate causation nor did we apply an (additional) weight or rating for the weight of evidence (WoE) in drawing up the overview of health effects. Considering that at present there is no accepted framework to judge causation for EDCs or consensus on a WoE approach to assess EDCs, it is important to emphasize here that the health endpoints included in this report are assumed *potentially related* or *associated* to EDCs. For those chemicals that are currently in use and suspected of ED properties, a WoE approach should ideally be applied that combines toxicological and epidemiological evidence. However, this combined interpretation of toxicological and epidemiological evidence is complex and challenging. Moreover, epidemiological evidence or data should not be a leading factor for identification of new EDCs, because epidemiological evidence can only be generated for chemicals that are already placed on the market, and is obviously not available for new chemicals. It is important to note that several suggested EDC-related human adverse health effects, are not covered within test guidelines for chemicals to obtain regulatory admission of chemicals to the market. Together, these issues clearly hamper the assessment of EDC-related health effects.

Evaluation of studies that quantified socio-economic costs of EDC-associated health effects

Recently, three (series of) studies have been published that quantify costs of health effects associated to exposure to EDCs: The Nordic Council report, commissioned by the Nordic Council of Ministers (Olsson et al., 2014), Health and Environment Alliance (HEAL) published a report with calculations performed by Bath University (HEAL, 2014) and thirdly, a peer-reviewed publication series led by L. Trasande, M.D. (NYU School of Medicine), was written by various leading scientists in the field and published by the Endocrine Society (Bellanger, Demeneix, Grandjean, Zoeller, & Trasande, 2015; Hauser et al., 2015; Legler et al., 2015; Trasande et al., 2015). In this report, these three EDC-related socio-economic cost studies were compared with regard to their methodology to quantify EDC-associated health cost and their results. All three aforementioned studies share a common scope, currency and timing: they cover the EU28, and were published in 2014 and early 2015. In total, thirteen EDC-associated health effects were quantified in these studies. There is a

distinct overlap between the endpoints that have been assessed in the study of HEAL and publication series of Trasande and co-authors, while the Nordic Council only assessed effects on male reproductive health. For each described EDC-associated health effect, a detailed evaluation was carried out of the underlying cost-of-disease studies, calculations, data on numbers of cases of disease (incidence/prevalence) and adjustment of costs. The detailed results on the evaluated parameters are combined in a single spreadsheet, which is provided as Annex B of this report. A summary of the main results and methodological approaches of the three studies is presented in Table 5 of this report.

To quantify the contribution of EDCs to a certain health effect, it is essential to set an accurate estimate for the etiological fraction (the attributable fraction, AF) or the % of the cases with a certain disease that can be linked to EDCs. It is generally acknowledged that the exact contribution of EDCs to the total disease burden is unknown, as is also often the case for other contributing genetic, lifestyle and environmental factors. The published studies used two distinct methodologies to establish an EDC-attributable fraction: HEAL and the Nordic Council both used fixed estimates (of 2/5% and 2/20/40%, respectively). In contrast, Trasande and co-authors calculated EDC-attributable cost based on exposure-response relations (ERRs) from epidemiological studies for specific compounds. This publication series also took the strength of evidence of combined strength of toxicological and epidemiological evidence (causation) into account in modelling an overall cost estimate.

For some health effects, the socio-economic cost estimates are similar, which is noteworthy given the fact that different methodologies and input parameters were used to obtain these estimates. For instance, the estimation for cryptorchidism-related costs is very similar among the three studies. For male reduced fertility, however, the costs calculated by the studies of Trasande and co-authors are more than an order of magnitude higher compared to the results of HEAL and the Nordic Council. Similarly, Trasande's calculated cost of AD(H)D are much higher compared to the calculation of HEAL, while HEAL's calculation of autism is very high compared to Trasande's estimate. However, irrespective of the quantitatively different outcomes, all three studies concluded that the estimated socio-economic cost of EDC-associated health effects are substantial with best estimates in the range of billions of euros for the whole EU28 on a yearly basis.

Assessment of gaps and needs and way forward using a 'modular approach' on cost of EDC-associated health effects

In this report, more than 80 different (potentially) EDC-associated health endpoints were identified, for 13 of which cost were quantified in aforementioned studies. This leaves a large part of the EDC-associated health effects unquantified. These mainly comprise of female reproductive effects, immune-related disorders and "other" EDC-related disorders (such as thyroid effects and neuroendocrine diseases).

To enhance interpretation and comparability between estimated cost of different health effects, structure, transparency, uniformity and completeness of information on socio-economic cost estimates is needed. Therefore, a so-called "modular approach" is proposed in this report that consists of "building blocks" of information on EDC-associated diseases and their socio-economic impacts. To set up the modular approach, information is proposed in this report that is deemed relevant for the interpretation of cost. These include general information on the etiology and

treatment of the disease, information on the state of knowledge on suspected chemicals, ED-mechanisms and pathways, co-morbidities, current incidence or prevalence of the disease. Finally, socio-economic cost estimates need to include published literature references and type of costs taken into account (direct, indirect and intangible cost) in order to interpret completeness of the cost data and compare results with other studies and health effects. By means of an explorative literature search of cost-of-disease studies, we found 48 health effects that have ever been quantified, irrespective of the link with EDCs. For 21 health endpoints, no or limited studies were identified that quantified healthcare cost. Based on available data, a total cost estimate for a given disease can be made and (where needed) extrapolated for EU28. Ultimately, the EDC-attributable fraction has to be applied to calculate the annual EDC-attributable cost for EU28.

One of the challenges is to attribute a certain etiological (or attributable) fraction (AF) of the total disease cost, to a single cause, in our case exposure to EDCs. This is challenging because exact causes of disease development are usually not known, and often considered to be a complex interaction of e.g. genetic, dietary, environmental, occupational and behavioral aspects. For our modular approach, we used 1%, 2,5% and 10% as best estimate EDC-attributable fractions. The 1 and 2,5% point estimates are within the (lower) environmental AF ranges presented in the papers of WHO and OECD, both for general environmental factors as well as for the contribution of pollution or chemicals specifically. We used a 10% as a high level estimate of the EDC-attributable fraction. This 1-10% range accounts for uncertainties for the role of EDCs in disease development, yet recognizes that for some diseases the role of environmental factors is stronger than for other diseases.

The modular approach was applied to a selected group of proposed EDC-associated health endpoints that have not been modelled before (endometriosis, neural tube defects and asthma), and two health endpoints quantified earlier (ADHD an ASD). The selection of these effects was based on expert judgement and team discussions on severity of the disease, incidence or prevalence, observations in the trends of incidence or prevalence, and availability of good-quality cost studies and other cost expertise. As stated earlier, WoE for the causation between these health effects and EDCs was not assessed. Literature searches were performed to select the best applicable cost studies in terms of year of publication, relevance of country, inclusion of direct and indirect costs. As an essential aspect of the modular approach, a breakdown of socio-economic cost for the three newly calculated EDC-associated health effects is shown (Table 8 of the main report). Using the defined EDC-attributable fractions of 1%, 2,5% and 10%, EDC-attributable costs for neural tube defects were estimated to be € 19 (7,7-76,5) million, for endometriosis € 2 (0,8-7,8) billion, and for asthma € 0,4 (0,2-1,7) billion. Together, these three health effects add € 2,4 billion (€ 1-10 billion) to the earlier estimated socio-economic costs of EDCs.

In this report, data is provided on potential EDC-attributable socio-economic cost that have (not) been addressed in earlier studies, as well as information that is relevant for the interpretation of cost estimates. The modular approach can help in further assessment of diseases that are associated with EDCs and allows new diseases, disorders and conditions to be added to this overview, along with an estimate of their potential socio-economic costs. We propose to visualize the information in a structured manner by means of a factsheet per health effect. Over time and to meet specific needs, different types of information (categories) could be added, deleted or changed on the factsheets. Furthermore, the information on the factsheets should be updated on a regular basis to stay up-to-date and include the latest (scientific) insights. Consequently, our proposed modular approach will

gradually lead to a more complete understanding of the potential socio-economic costs of EDC-associated diseases and will help to prioritize (regulatory) actions and further research on the basis of health impact and societal costs. This methodology could also be applied in a broader perspective, to analyze any other health impact, potentially causal agent, and associated socio-economic costs.

Overall evaluation of EDC-associated health effects and socio-economic costs

This report provides an overall evaluation of the available data on EDC-associated health endpoints and related socio-economic cost as well as new cost estimates. These cost estimates have been used to determine a cost range for each health effect and a total range for the EU28. **The total estimate of socio-economic burden of EDC-associated health effects for the EU28 ranges between 46 and 288 billion € per year.**

Although only a few of the suggested EDC-associated health effects have been quantified, this report can help to prioritize future research and actions for the assessment of potential EDC related adverse health effects and costs. Using a cost-based approach can also help in the priority setting of the development and inclusion of test guidelines for EDCs that address certain types of diseases in regulatory frameworks. Based on this report, these should at least include neurodevelopmental toxicity, diabetes, obesity and immunological disorders. Neurodevelopmental and -behavioral diseases and disorders comprise the largest contributors to the total EDC-associated socio-economic cost estimates. This group of neurobehavioral disorders includes several pervasive disorders that persist for a lifetime, thereby leading to in prolonged costs. Here, especially the contribution of IQ loss (€ 32-184 billion) dominates the cost estimate. It was shown that almost every newborn child could lose some IQ points due to (mostly) prenatal exposure to EDCs. It should be noted, however, that socio-economic impact of IQ loss is calculated based on indirect loss, *i.e.* income loss due to lower IQ and hence does not represent actual expenditures (such as medications and treatments). Apart from IQ loss, the cost for other neurodevelopmental and -behavioral health effects are also estimated to be relatively high compared to other groups of health effects that are associated with EDCs. These cost largely comprise of direct healthcare cost, provided by specialized institutes and residential care. The cost of the group of metabolic diseases is also estimated to be relatively high, with € 1,6 to 17 billion for obesity and € 1,4 to 17 billion for diabetes type 2. This is especially due to a large prevalence of diabetes and obesity within society. The group of immunological diseases, disorders and conditions has not been sufficiently quantified yet, which hampers (EDC-associated) socio-economic cost estimation. Especially considering the increasing incidence in immunological diseases, such as asthma and allergies, and probable contribution of EDCs in these disease etiologies, this clearly needs further study. However, at present, legislative frameworks for screening of chemicals do not obligate to screen for (developmental) neurotoxicity nor metabolic or immunological endpoints. Moreover, it would be very useful to evaluate if current chemical testing guidelines even sufficiently cover endpoints related to these diseases.

This report indicates that even when taking the low-range estimates, the estimated EDC-associated health costs may be substantial. In view of these substantial estimated socio-economic costs but also considering the uncertainties surrounding the health effects of EDCs, more studies to identify EDC-related health effects, strength of evidence, endocrine mechanisms, mode of actions, and attributable fractions to a specific health effect are desired. As such, this report should help prioritization of actions on EDCs and areas for future research.

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1. Introduction to Endocrine Disrupting Chemicals

1.1. What are Endocrine Disrupting Chemicals?

Our endocrine system regulates and drives growth, development, homeostasis and reproduction (amongst others). The endocrine system consists of various hormone producing glands and hormone producing organs and tissues, such as kidney, liver, heart, gonads and body fat. Physiological effects of hormones and feedback pathways towards hormone producing glands, organs and tissues is provided via receptors, which induce a cascade of effects often via interaction with the DNA.

The endocrine system is very sensitive and hormones already act at very low concentrations. There is now substantial toxicological and epidemiological evidence that certain chemicals have the ability to interfere with and modulate the endocrine system in humans and wildlife. Although there is ongoing discussion within the EU on the exact definition of a (potential) Endocrine Disruptive Chemical (EDC), the definition by the World Health Organization and the International Programme on Chemical Safety (WHO/IPCS) from 2002 is still most commonly used: *"An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations. A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations."*(Damstra T., Barlow S., Bergman A., Kavlock R., & Van Der Kraak G., 2002).

Exposure to EDCs in humans has been related to a whole spectrum of diseases and deficits, including metabolic diseases, certain hormone-dependent tumors, neurobehavioral deficits and male reproductive deficits (A. Gore et al., 2015). However, the weight of evidence for a causal relationship is still a topic of intense scientific debate.

Well-known examples of chemicals that are associated with endocrine disruption (ED) include polybrominated diphenylethers (PBDEs), organophosphorus pesticides (OPs), phthalates, bisphenol-A (BPA) and their analogues, as well as the "older" persistent organic pollutants (POPs) such as dichloordifenyltrichloorethaan (DDT), chlorinated dioxins and polychlorinated biphenyls (PCBs). Exposure to many of these chemicals is still ubiquitous. Numerous papers have shown that these chemicals can be detected in e.g. our body fat, breast milk, blood, cord blood, and urine. However, it has also been demonstrated that remedial actions for certain compounds by governments and/or from manufacturers over the past decades has resulted in a decreased body burden in humans for these specific compounds, e.g. for dioxin-like compounds (Rylander, Rignell-Hydbom, Tinnerberg, & Jönsson, 2014). As part of this remedial process, alternative chemicals have been introduced on the market, but for many of these novel compounds it is not known whether these can have a modulating effect on the endocrine system (Rylander et al., 2014). As a result, present exposure to potential EDCs is still subject to uncertainty and a substantial scientific and public debate and concern.

1.2. Current discussion on EDCs

The impact of (potential) EDCs on human health and the environment is an area of extensive debate and includes discussions on the definition of an "endocrine disruptor", the criteria to identify chemicals as an EDC, type of related health effects, weight of evidence, mechanisms, methodology

for risk assessment and regulatory approach. Over the years, this debate has become more and more polarized. At one side there are scientists who are concerned about EDCs, who point at increasing evidence that current risk assessment methodologies are not sufficiently protecting human and animal health, and call for action partly based on precautionary principles as well as observational health studies in humans and wildlife (Diamanti-Kandarakis et al., 2009; A. Gore et al., 2015; The Berlaymont Declaration, 2013). A major concern is that EDCs may act at very low concentrations, which is not sufficiently investigated in animal studies that typically use high-dose levels. Moreover, low-dose effects might be different from high-dose effects. Additionally, several human-relevant effects and sensitive periods of exposure and exposure to chemicals and mixtures of EDCs are not adequately addressed in current hazard assessment practices. As a consequence, these scientist argue that safe exposure levels for (potential) EDCs established using traditional risk assessment processes are highly uncertain (The Berlaymont Declaration, 2013). On the other side, there are scientists, who oppose the conclusions and concerns published in reviews on EDCs by the UNEP, WHO and European Commission. These critics put emphasis on the uncertainty of causality and suggested relationships with health effects of (potential) EDCs especially in humans. They also argue that the current risk assessment approaches that use a no-effect threshold from animal studies is also applicable to EDCs (Autrup et al., 2015; Lamb et al., 2014; Nohynek, Borgert, Dietrich, & Rozman, 2013). Subsequently, these publications have provoked rebuttals from scientists who have raised their concerns about EDCs (A. Bergman et al., 2013; A. Bergman et al., 2015; A. C. Gore et al., 2014; Kortenkamp, Martin et al., 2012; R. T. Zoeller et al., 2014). This discussion has further been complicated by interference and statements from chemical industry (ACC, Cefic, CLA, CLC, CLI, ECPA, 2014; ECPA, 2014) and accusations for conflicts of interest due to relationships with industry (Horel & Bienkowski, 2013).

This debate has hampered regulatory action on (potential) EDCs. Currently, the European Commission is carrying out an impact assessment, which seems to slow down the process to set criteria for identifying EDCs and phasing out existing chemicals on the market that might have endocrine disruptive properties. In addition, the adequacy of current testing frameworks (e.g. under REACH, PPPR and the Biocide Regulation) to capture an endocrine disruptive effects are being questioned, while at the same time newly developed testing methodologies are not easily included in legislative frameworks. Both the acceptance of such additional tests as the difficulty to include those tests for endocrine disruption in the various legislative frameworks is bogging down possible regulatory actions on chemicals with unknown potential ED properties that are already being produced and used, and new market introductions. Considering the increasing trends in endocrine-related diseases (Kortenkamp, Evans et al., 2012; UNEP/WHO, 2013) and the yearly high production of industrial chemicals with toxic and/or posibble ED effects (Eurostat), risk managers and regulators need to be well-informed on the potential consequences of the (lack of) regulatory actions with respect to EDCs.

1.3 Risk appraisal and socio-economic impacts of EDCs in the light of risk governance

So far, much attention went into the debate whether or not a causal relationship exists for EDCs and various adverse health effects. However, this is only one part of the body of information on which policy decisions can be made. The International Risk Governance Council (IRGC) states: "Policy makers are often required to make decisions and take actions under considerable time pressure,

with incomplete information and often faced by conflicting advice. Even in situations of knowledge deficit decisions must be made and action is often needed" (IRGC, 2012).

What if we look to "the issue of EDCs" as if it was any other risk? The IRGC framework, which aims to understand, analyze and manage important risk issues, comprises five linked phases: pre-assessment, risk appraisal, characterization and evaluation, management, communication (IRGC, 2012). In our report, we will focus on (parts of) risk appraisal and characterization and evaluation as defined by the IRGC.

Risk appraisal develops and synthesizes the knowledge base for the decision on whether or not a risk should be taken and, if so, how this risk can possibly be reduced or contained. As part of the risk appraisal, a scientific assessment should be carried out as well as a concern assessment. Within the scientific assessment, one of the key questions to be answered is "What are the potential damages or adverse effects?" In this report, we will focus on this question.

Next, the phase of characterization and evaluation is intended to ensure that the evidence based on scientific facts is combined with a thorough understanding of societal values when making the sometimes controversial judgment of whether or not a risk is "acceptable", "tolerable" or, in extreme cases, "intolerable" and, if so, to be avoided. One of the questions in this phase is "What are the societal, economic and environmental benefits and risks?". From an industry point of view, additional testing for endocrine disruption will have a financial burden, as well as other restriction measurements arising from testing results. From a societal point of view, however, cost are carried if adverse effects will contribute to the burden of disease. In this report, we aim to provide a better insight in the potential socio-economic impacts of EDC-associated health effects.

1.4 Objectives of this report

Our overall goal is to provide improved understanding on the potential socio-economic cost of EDC-associated health effects. The assessment of a causal association between EDC exposure and health effects is outside the scope of this report and will therefore not be discussed. Here, we aim to identify and address gaps and needs in availability and quality of information that are relevant for health impacts analysis and modelling of socio-economic cost that have been associated with EDCs. As such, we summarize, compare and evaluate the available information on EDC-associated health endpoints and existing modelled socio-economic costs. In order to deal with identified information gaps, we propose a modular approach to include additional calculation of socio-economic cost and add relevant information on EDC-related diseases. This approach is exemplified for five EDC-associated health effects.

This report consists of four major parts:

- Inventory of EDC-associated health effects (Chapter 2);
- Evaluation of studies that quantified socio-economic costs of EDC-associated health effects (Chapter 3);
- Assessment of gaps and needs and way forward using a 'modular approach' on cost of EDC-associated health effects (Chapter 4);
- Overall evaluation of EDC-associated health effects and socio-economic costs (Chapter 5).

2. Inventory of health effects potentially related to exposure to endocrine disrupting chemicals

The past years, the EU, WHO, UNEP and other institutions and groups of scientist have published leading reviews on EDCs that include an overview of EDC-related diseases, disorders and conditions. In addition, these reviews address mechanisms and modes of action (MoA) and strength of evidence from a toxicological and epidemiological point of view (Å Bergman et al., 2013; Diamanti-Kandarakis et al., 2009; European Environment Agency, 2012; Kortenkamp et al., 2012; The Berlaymont Declaration, 2013; UNEP/WHO, 2013; WHO, 2014). There is substantial agreement on which categories of health effects in which EDCs are considered to play a role, e.g. reproductive health effects and neurodevelopmental effects. However, depending on the focus of the reviews and requirements for inclusion, there are also differences in what specific health endpoints are associated with EDC effects. In this chapter, we remove overlap and differences in specific health effects mentioned in the prevailing literature, with the aim to provide an as much as possible complete and clear overview of health endpoints related to exposure to (potential) EDCs.

2.1. Scope for inventory of EDC-associated health effects

In this assessment, we focus on listing the potential adverse impacts of EDCs to give an as much as possible complete overview of health effects (potentially) related to exposure to EDCs. Health effects (also called health endpoints) could be diseases, disorders or conditions, yet these are not further distinguished in this report.

The overview is generated based on the health effects mentioned in peer-reviewed literature reviews on EDCs, and limited additional studies. Causality to each health effect is extensively addressed in the underlying reviews and not further addressed in the overview in this report. In drawing up the overview of health effects, we did not apply an (additional) weight or rating for evidence (often referred to as weight of evidence, WoE). It is outside our scope of this report to discuss the underlying epidemiological and toxicological evidence from peer-reviewed publications used. However, we will discuss the issues concerning establishing a causal association in paragraph 2.3.

Taking into account the enormous amount of published studies on EDCs and the current speed of progress in toxicological and epidemiological studies that focus on this field, such an overview of EDC-related diseases should still be considered tentative as new scientific evidence and insights seem to develop continuously.

2.2. Methodology

The list of scientific publications on EDCs and their (potential) effects and mechanisms is extensive, with over 10.000 studies published and listed in search engines. Within the limited timeframe for preparing this report, no systematic review could be performed of these studies. To provide an as much as possible complete overview of EDC-related health endpoints, authoritative reviews on EDCs and their effects, published in the past 6 years by institutions such as WHO, UNEP and the EU, were used to provide a list of (potential) EDC-related health effects. These studies have assessed whether a certain involvement of the hormone system is confirmed or biologically plausible, and if evidence from toxicological and/or epidemiological studies is available to support a relation with EDCs. We

acknowledge that the studies used different criteria to determine weight of evidence and/or causality to establish a role for EDCs in specific health effects. For more information, the reader is referred to the original studies, as it is beyond our scope to evaluate these criteria. Considering that at present there is no accepted framework to judge causation, it is important to emphasize here that the included health endpoints in this report are assumed *potentially* related to EDCs.

The following reviews have been included for the search for EDC-related health endpoints:

- Diamanti-Kandarakis E *et al.*, 2009. EDC-1: Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews* 30(4):293-342
- Gore A.C. et al., 2015. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine Reviews* 36(6):E1–E150
- European Commission, 2012: Kortenkamp A *et al.*, 2012. State of the art assessment of endocrine disruptors. Annex I: Summary of the state of science, revised version 2012. European Commission Project Contract Number 070307/2009/550687/SER/D3
- UNEP/WHO, 2013. State of the science of endocrine disrupting chemicals 2012 / edited by Åke Bergman, Jerrold J. Heindel, Susan Jobling, Karen A. Kidd and R. Thomas Żoeller.
- WHO Regional office Europe, 2014. Identification of risks from exposure to endocrine-disrupting chemicals at the country level. Edited by: Dr Nida Besbelli, Dr Irina Zastenskaya
- European Environmental Agency (EEA), 2012. The impacts of endocrine disrupters on wildlife, people and their environments. EEA Technical Report 02/12012. ISSN 1725-2237

With exception of the EDC-2 report published in November 2015, all other large reviews were several years old at the time of writing this report. Due to the rapidly evolving scientific knowledge, we have used additional, more recent literature to further specify two immunological categories of health effects listed in the authoritative reviews above ('increase of local infections' and 'autoimmune diseases').

2.3. Results

Table 1 gives an overview of health effects that are associated with EDC exposure in the literature. This list includes all diseases, disorders and conditions that were mentioned in at least one of the studies described in paragraph 2.2. Some health effects were listed by (almost) all reviews, while other effects were only considered by one or two of the peer-reviewed studies. Still, there is a considerable agreement on the categories of health effects that are linked to endocrine disruption. Most consistency among reviews seems to exist within the group of reproductive health effects and group of hormonal cancers. Listing of individual health effects is less consistent in the group of immune system disorders and the group of "other" disorders and conditions. However, it is noted that (almost) all groups of health effects are covered in the different reports. Annex A provides a detailed overview with references to the different literature reviews per health effect and references to more recent studies that were not captured in the reviews.

Clustering of health effects

A total of 82 health effects that may be associated with EDCs were identified from the literature. These endpoints can be clustered into six major categories: reproductive health, hormonal cancers, neurodevelopmental syndromes and conditions, effects on the metabolic system, immune system disorders and one mixed group of "other" health endpoints. Some health endpoints could be placed

in more than one category, but for the sake of clarity the most prevailing option was chosen for this report. For example, an autoimmune thyroid disease is listed among autoimmune diseases in the group of immune disorders, but it could also be listed under thyroid diseases in the cluster of "other" health endpoints.

Definitions of effects

The health effects in Table 1 predominantly reflect those mentioned in the various literature reviews. As a result, there is some overlap between health endpoints, e.g. childhood lymphoma (which could be any type of lymphoma) and non-Hodgkin lymphoma (found both in children and adults). Furthermore, health endpoints may arise from a similar underlying mechanism, e.g. the Testicular dysgenesis syndrome (TDS) also comprises cryptorchidism, hypospadias, and reduced male fertility resulting from abnormal fetal testosterone exposure. All these effects are now listed as separate endpoints. Such a correlation can also be argued for e.g. obesity and the development of diabetes. Finally, some health endpoints may be observed in different directions depending on the mechanism of individual EDCs involved, e.g. female precocious puberty and delayed puberty. However, in order to retain the possibility to compare studies, we used as much as possible the definitions of health effects as defined in the reviews used.

Weight of scientific evidence for causation

One of the biggest topics of debate is the issue of causation, e.g. whether or not a causal link exists between exposure to (a) certain chemical(s), hormonal disruption, and adverse effects in an intact organism, or its progeny, or (sub) populations.

To provide a well-founded statement for a chemical being an EDC, careful selection, evaluation and combination of experimental *in vitro* and *in vivo* studies are needed. In view of the fact that current animal studies do not cover all relevant endpoints observations, human epidemiological data are of utmost importance. *In vitro* studies can for example provide mechanistic basis to describe the potential of a chemical to bind or (ant)agonise the action of hormone receptors or other disruption of endocrine pathways. Animal studies would give biological plausibility that endocrine disruption may also occur *in vivo*, and could link exposure levels to certain apical health effects. However, many suggested EDC-linked human adverse health effects, such as those listed in Table 1, are not covered within current guidelines for chemical testing to obtain regulatory admission of chemicals to the market. This is an acknowledged gap in current legislation. For example, the Endocrine Disrupters Expert Advisory Group (ED EAG) of the Joint Research Centre (JRC) of the EU stated that existing standardized assays might miss some endpoints sensitive to endocrine disruption, and acknowledged that there was no standardized assay currently available in mammals that allows the investigation of early life/in utero exposure on effects that may appear in later life stages, such as cancer, impact on menopause and senescence (Munn & Goumenou, 2013).

Table 1. Inventory of EDC-associated health effects from peer-reviewed reviews on EDCs, and some recent studies (in *italic*). The references can be found in Annex A. Health effects in blue represent effects for which socio-economic cost have previously been quantified in other studies (Chapter 3). The health effects in green refer to effects for which costs are addressed in this report (Chapter 4).

1. Reproductive health

Female reproductive problems

- Female fecundity and fertility
  - Reduced female fecundity (lower number of offspring)
  - Reduced female fertility
  - Infertility
- Adverse pregnancy outcomes
  - Ectopic pregnancy
  - Spontaneous abortions (miscarriages)
  - Hypertensive disorders of pregnancy, incl. pregnancy-induced hypertension and pre-eclampsia
  - Intrauterine growth restriction (IUGR)
  - Preterm delivery
  - Low birth weight or length
  - Birth defects
  - Disturbed (decreased) lactation period
- Polycystic ovarian syndrome (PCOS)
- Endometriosis
- Reproductive tract abnormalities
  - Uterine fibroids
  - Abnormal vaginal, cervical, uterine, and oviduct anatomy
  - Ovaries: Premature ovarian failure (POF), decreased ovarian reserve/increased atresia, aneuploidy, granulosa steroidogenesis, altered primordial follicles, follicle growth, oocyte quality
  - Vaginal adenosis (benign abnormality)
- Premature thelarche
- Female idiopathic precocious puberty / early menarche
- Female delayed puberty
- Disturbed menstruation cycle (Oligomenorrhea)
- Early age at menopause

Male reproductive problems

- Cryptorchidism
- Hypospadias
- Other male reproductive organ abnormalities (reduced testis weight, abnormal small penis, problems efferent ducts, altered AGD, morphology of seminiferous tubules, nipple retention)
- Declining fertility due to reduced semen quality (abnormalities) and quantity (oligospermia)
- Testicular dysgenesis syndrome (TDS)
- Epididymal cysts (infection/inflammation of the tube that carries semen out of the testicle)
- Orchitis (infection/inflammation of testis)
- Male delayed puberty
- Prostatic intraepithelial hyperplasia (PIN)
- Prostatitis (prostate inflammation)

2. Neurodevelopmental syndromes and conditions

Neurobehavioral disorders

- Autism spectrum disorders (ASD)
- AD(H)D; attention deficit (hyperactivity) disorder
- IQ loss
- Mental retardation
- Cerebral palsy
- Neural tube defects
- Psychomotor retardation, memory, learning problems
- Depressive disorders
- Behavioral problems: social, aggression, anxiety, sexual

3. Hormonal cancers

Hormone-related cancers

- Breast cancer
- Endometrial cancer
- Ovarian cancer
- Clear cell adenocarcinoma of the vagina and cervix uteri
- Prostate cancer
- Testis (testicular germ cell) cancer
- Thyroid cancer

4. Effects on the metabolic system

Metabolic syndromes

- Obesity (child and adult)
- Diabetes mellitus (type 2)
- Diabetes type 1
- Metabolic syndrome

Cardiovascular system

- Cardiovascular disease (direct and indirect)
- Cardio protection
- Hypertension

5. Immune system disorders

Immune function, immune diseases and disorders

- Increase of systemic infectious diseases due to altered immune response
- Increase of local infections due to altered immune response
  - Periodontal disease
  - *Otitis media*
  - *Respiratory tract infections*
  - *Exanthema subitum*
- Allergies other than asthma: allergic rhinitis, allergic conjunctivitis and atopic dermatitis (eczema)
- Autoimmune diseases (incl. thyroid disease)
  - Autoimmune thyroid disease (AITD) (e.g. Hashimoto's thyroiditis, Graves' disease)
  - Multiple sclerosis (MS)
  - *Systemic lupus erythematosus (SLE)*
  - *Rheumatoid arthritis*
  - *Ulcerative colitis*
- Asthma, childhood asthma, wheeze
- Myalgic encephalopathy/chronic fatigue syndrome/post viral fatigue syndrome (ME/CFS/PVFS)
- Fibromyalgia (rheumatic disorder)

Hematopoietic disorders and malignancies

- Childhood lymphoma
- Leukemia
- Non-Hodgkin lymphoma

6. Other disorders and conditions

Population effects

- Increment death rate among men due to lower testosterone
- Sex ratio - declining male population

Neuroendocrine disruption

- Various diseases that affect the pituitary or hypothalamus

Adrenal disorders

- Adrenocortical hyperplasia (growth, stress response)
- Cushing's disease

Thyroid disruption

- Adult (sub)hypothyroidism
- Congenital hypothyroidism (causing mental retardation)
- Thyroid resistance syndrome

Bone disorders

- Increased risk of bone fractures
- Osteoporosis
- Other bone disorders (e.g. orthopedic defects, irregular calcifications)

Epidemiological evidence may reveal causal links with (not previously established) EDC-related diseases, because *in vitro* and *in vivo* experiments may not cover relevant events as described above, or effects from laboratory experiments are not representative of the human situation. As such, epidemiological studies would provide insights whether health effects are seen under realistic exposure conditions in human populations. Yet, considering the large variation in the human population with respect to genetics, socio-economic impacts and environmental influences, including dietary habits and chemical exposures, it is difficult to establish strong correlations between adverse health effects and often low concentrations of potential EDCs. Moreover, epidemiological evidence or data should not be a leading factor for identification of new EDCs, because epidemiological evidence could only be generated for chemicals already placed on the market, and will not be available for new chemicals. It would be unethical to wait for strong epidemiological evidence for adverse and potentially irreversible health damage in intact organisms and/or (sub) populations before a chemical is acknowledged to be an EDC.

For those chemicals that are currently in use and suspected of ED properties, a weight of evidence (WoE) approach should ideally be applied that combines toxicological and epidemiological evidence. However, this combined interpretation of toxicological and epidemiological evidence is complex and challenging. Already in the 2002 WHO report, a collective WoE approach has been proposed based on principles for defining cause-and-effects relationships (Damstra T. et al., 2002). Also in the 2012 report from the EU, the need for consensus on assessment of the WoE was stressed (Kortenkamp et al., 2012) and a systematic element using tables with criteria was introduced. The UNEP/WHO provided a narrative summary in their report on the proof of scientific evidence for endocrine disruption for various health endpoints (UNEP/WHO, 2013). In parallel, industry members also made scientific proposals for a WoE approach (Bars et al., 2011; Borgert et al., 2011). The EU set up an Endocrine Disrupters Expert Advisory Group (ED EAG) that aimed to evaluate key scientific issues relevant to the identification and characterization of endocrine disrupting substances (Munn & Goumenou, 2013). The ED EAG supported consideration of mode of action and adversity (via adverse outcome pathways: AOP) in parallel applying weight-of-evidence approaches, weighing all available evidence, both positive and negative, including human epidemiology data, field data, animal experimental (eco)toxicology studies, *in vitro* data, (Q)SAR, analogue and category approaches to reach a conclusion on ED properties (Munn & Goumenou, 2013). However, despite these efforts, consensus on which chemicals could be identified as EDCs or a framework on the WoE, strength of evidence, or proof for causation for adverse effects does still not exist. It is questionable whether consensus in the near future can be expected due to differences in interpretations of evidence by different groups of scientists and stakeholders such as chemical industries, NGOs and governments.

In addition, there are also other issues that hamper a consensus on a WoE approach for EDC-related health effects, including the following:

- Each health effect can be linked to various chemicals or even a specific mixture effect, each with a different burden of scientific evidence;
- The other way around, chemicals may interrupt various endocrine pathways, and could therefore relate to different health effects;
- *In vitro*, *in vivo* and epidemiological studies are hard to compare due to differences in e.g. methodology, (sub)populations, exposure levels and conditions;

- A flaw in methodology or analysis can result in a false negative or positive effect. For instance, susceptible windows of exposure or effects at low exposure levels are often not taken into consideration in both experimental and epidemiological studies, especially the older studies. Consequently, a chemical may falsely be labeled as non-EDC.
- For the majority, if not all, chemicals a robust toxicological dataset is lacking. None of the current regulatory frameworks within the EU requires mechanistic information in their basic requirements or crucial information on apical endpoints such as developmental neurotoxicity and immunotoxicity;
- For those (thousands of) chemicals currently in production and use there is a general lack of biomonitoring data and well-designed epidemiological studies that take into account susceptible windows of exposure;
- There is a risk for publication bias. Whether results on adverse effects of chemicals are published or not might be influenced by the funding agency, such as governmental bodies or industry. There are some illustrative examples for the so-called funding effect, e.g. for test outcomes on BPA (Vom Saal & Hughes, 2005).

3. Evaluation of EDC-associated cost studies of The Nordic Council, HEAL, and Trasande *et al.*

Recently, several reports have been published that quantify costs of health effects related to exposure to (potential) EDCs. The Nordic Council has calculated for EDC-related male reproductive health disorders only, the cost in the EU28 is € 600 million (€ 59-1200 million) per year of exposure (Olsson et al., 2014). In the two other studies, the annual EDC cost estimates for various health impacts in the EU28 had a range of € 13 to 31 billion (HEAL, 2014) and a best-cost estimate of € 157 billion (90% C.I. € 32-212 billion) (Trasande et al., 2015). Irrespective of the quantitatively different outcomes, all three studies revealed that socio-economic cost of EDC-related health effects could potentially be substantial and best estimates are in the range of billions of euros for the whole EU on a yearly basis.

3.1. Scope of evaluation

In this chapter, three previously published EDC-related socio-economic cost studies are compared with regard to their methodology to quantify EDC-associated health cost and their results. We aim to explain differences in estimated cost and to obtain an improved understanding and interpretation of the health effects and socio-economic impacts of EDCs in the EU. For that, we have evaluated:

- The type of health effects studied;
- The general methodology to quantify EDC-related health effects;
- The results of the socio-economic costs per EDC-related health effect and in total;
- The underlying data on cost of diseases, especially what type of cost (direct, indirect, intangible) have been included in the estimate;
- Cost corrections and adjustments made in the reports;
- The underlying data for an estimate of population size affected (use of EDC-attributable fractions, incidence- or prevalence rate).

3.2. Methodology

Table 2 presents the three main (series of) publications that have addressed the socio-economic costs of EDC-related health effects. The Nordic Council report was commissioned by the Nordic Council of Ministers and executed by Olsson and co-authors. The calculations in the HEAL report were performed by Bath University. The Trasande series was written by various leading scientists in the field and published, after peer-review, by the Endocrine Society. All studies share a common scope, currency and timing: they all cover the EU28, and were published in 2014 and early 2015.

Table 2. Overview of studies that have evaluated socio-economic cost of EDC-associated health effects

Publication (series)	Referred to in this report as:	Full title of publication	Reference
The Nordic Council of Ministers	The Nordic Council	The cost of inaction – A socio-economic analysis of costs linked to effects of endocrine disrupting substances on male reproductive health.	Olsson et al., 2014
The Health and Environment Alliance (HEAL)	HEAL	Health cost in the European Union: How much is related to EDCs?	HEAL, 2014
Trasande and co-authors	Trasande *et al.*	Estimating burden and disease cost of exposure to endocrine-disrupting chemicals in the European Union	Trasande et al., 2015
	Hauser *et al.*	Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union	Hauser et al., 2015
	Legler *et al.*	Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union	Legler et al., 2015
	Bellanger *et al.*	Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union	Bellanger, Demeneix, Grandjean, Zoeller, & Trasande, 2015

For analysis of these studies, a coarse-to-fine evaluation approach was applied and no additional modelling, adjustment or extrapolation was carried out. Firstly, general information and outcomes of the three EDC-cost of disease studies were evaluated. This includes the type of quantified health effects, the general methodology of the study, and the results on EDC-related cost estimates per disease. Next, the origin and composition of the resulting costs were evaluated to explain possible differences in cost estimates per disease and improve the understanding of presented socio-economic costs. To do so, the scope and study parameters from underlying cost-of-disease studies from literature were collected. This includes the type of direct, indirect and intangible costs quantified for the specific disease. Furthermore, some of the original studies have been adjusted by the Nordic Council, HEAL, and Trasande and co-authors to suit their EDC-specific scope (e.g. adapted to relevant currency, population etc.). Lastly, estimates of EDC-attributable cases (or fractions potentially related to EDC-exposure) that could be associated with a specific disease and associated cost-of-disease were evaluated. The parameters for which information was collected are shown in Table 3.

Table 3. Parameters on which information has been collected to evaluate socio-economic cost of EDC-associated health effects. These parameters are found in original cost-of-disease study used (source literature on disease costs, most often not linked to EDCs) and EDC-cost studies that adapted original literature (HEAL, Nordic Council and Trasande *et al.*).

Type of parameter	Relevance	Parameters
General study parameters	These parameters provide information on the context in which the study was performed	- Author - Publication year - Year of data collection - Country of study - Per person estimate or total disease cost for society - Methodology: bottom-up or top-down assessment of costs - Subpopulation / study perspective - Currency and currency-year - Time horizon (e.g. lifetime cost, annual costs) - Discounting applied (yes/no and %)
Type of cost included in the cost estimate	The scope for the assessment of costs: which kinds of costs are included? Cost could be direct, which means these are 'real' expenses. Other costs are indirect, or even intangible.	- Direct healthcare cost (DHC): e.g. treatment (hospital, home care, institutes), medication - Direct non-healthcare cost (DNHC): e.g. travel cost to a clinic, childcare cost when receiving treatment, co-payments by patients - Indirect healthcare cost (IHC): loss of years living in good health (e.g. measured in Disability Adjusted Life Years - DALYs), cost of diseases otherwise avoided - Indirect non-healthcare cost (INHC): productivity loss patients and care-givers, social welfare payments (benefits) - Intangible cost (IC): dissatisfaction, loss of quality of life (e.g. measured in Quality-Adjusted Life Years - QALYs)
Adjustment and extrapolation parameters	The original cost-of-disease studies are adapted to suit the scope for EDC-related costs in the EU and enhances comparison and harmonization between health effects modelled	- To relevant currency and currency year - Adjustments for ratio of each country's Purchasing Power Parity (PPP) adjusted per-capita Gross Domestic Product (GDP) to create a country-specific estimate - Correction for double counting - Weighting of averages of various cost - To suitable age/life-time - Discounting, if not already included in original cost study (e.g. to calculate lifetime cost based on annual cost)
Cases with the disease (incidence/ prevalence)	Costs are dependent on the amount of cases with the disease	- Use of incidence (newly diagnosed cases of a disease) or prevalence (number of cases of disease existing in a population) - Relative amount of cases (% within population) - Total number of cases in EU28
Cases with the disease, attributed to EDCs	Amount of cases or fraction of total costs related to EDCs	- Use of fixed or calculated estimate of an EDC-attributable fraction - Amount of cases with the disease attributed to EDC-exposure

3.3. Quantified EDC-associated health effects

A comparison between the three major studies (HEAL, 2014; Olsson et al., 2014; Trasande et al., 2015) identified a total of thirteen common health effects that were quantified. Between the study of HEAL and publication series of Trasande and co-authors there is a distinct overlap between the endpoints that have been assessed (Table 4). It should be noted that HEAL considered the influence of male and female fertility together, while the Nordic Council and Trasande and co-authors considered only effects on male fertility.

Table 4. Overview of type of health endpoints quantified in the different EDC-related cost studies.

Cat.	Source publication		Nordic Council	HEAL	Trasande and co-authors
Reproductive tract and fertility					
1	Reduced female fertility			x[a]	
	Reduced male fertility due to reduced semen quality and quantity		x		x
2	Cryptorchidism		x	x	x
3	Hypospadias		x		
Neurobehavioral diseases and disorders					
4	Autism spectrum disorders (ASD)			x	x
5	AD(H)D (attention deficit (hyperactivity) disorder)			x	x
6	IQ loss				x
7	Mental retardation				x
Hormone-related cancers					
8	Breast cancer			x	
9	Prostate cancer			x	
10	Testis (testicular germ cell) cancer		x	x	x
Metabolic syndromes / other					
11	Obesity	Obesity child			x
		Obesity adult		x	x
12	Diabetes mellitus (type 2)			x	x
13	Increment death rate among men due to lower testosterone				x

[a] *male and female reproductive effects were assessed together*

3.4. General comparison of methodology

The methodological approaches for calculations of the costs of EDC-associated health effects of the three studies are presented in Table 5. This comparison of methodologies can explain some of the differences in estimation of costs for similar endpoints and can also be used for comparison and interpretation of the total cost estimates presented in our report.

EDC-related diseases modelled

The total cost estimate calculated by the Nordic Council is much lower compared to the other two studies. This is because the Nordic Council took only male reproductive effects into account, while the other two studies included many other potential EDC-associated health effects.

Table 5. Comparison of general methodological approaches between the selected studies that have addressed the socio-economic costs of EDC-associated health endpoints

Parameter		Nordic Council	HEAL	Trasande and co-authors
Health effects		Male reproductive disorders only	Various (see also table 4)	Various (see also table 4)
Current / future losses?		current and future costs	main focus: current costs	current and future costs
Approach for cost modelling		Own calculation, largely based upon Swedish patient registry.	From secondary literature	From secondary literature
Cost type included	**Direct cost**	Yes	Yes	Yes
	Indirect cost	Yes	where available (included for autism, breast cancer, prostate cancer and diabetes type 2)	where available (included for cryptorchidism, autism, AD(H)D, IQ loss and testicular cancer)
	Intangible cost	where possible (included for testicular cancer, hypospadias, cryptorchidism)	No	Where possible (included for testicular cancer, cryptorchidism, obesity)
Discounting rate	**Only for cost that occur in the future**	4% (direct+indirect cost) 1,5% (intangible cost)	Depending on study: 0%, 3% or 3,5%	Depending on study: 3% or 3,5%
Methodology to estimate EDC-attributable cost		Etiological fraction: 2%, 20%, 40%	Etiological fraction: 2%-5%	Calculated based on exposure-response relationships for specific chemicals (between 0,16 – 35,3% depending on health effect)
Correction for strength of evidence		No	No	Yes
Currency / currency year		€ / 2013	€ / 2012	€ / 2010 or 2012
Range of total results		€ 59 million - 1.2 billion	€ 13 - 32 billion	€ 45 – 270 billion
Best estimate		€ 591 million	€ 13 - 32 billion	€ 157 billion
Dominant contributor to total cost		Testicular cancer (40% of total cost)	Autism (35% of total cost)	IQ loss (69% of total cost)

Interpretation of costs

There is a slight difference in how costs should be interpreted between studies. For health effects such as hypospadias (genital malformation in baby boys) costs for treatment will occur shortly after birth. Here, assuming a role of EDCs in the origin of the disease, the time between exposure and treatment is limited. However, for some diseases that have a developmental origin, costs will occur after many years. Testicular cancer, for example, usually develops between the ages of 20 to 40, leaving a few decades between prenatal exposure to EDCs and the moment when costs are carried. Because future costs are generally valued lower than costs that are paid now, economist apply a rate of "discounting" to costs that manifest in the future. The rate of discounting varies between studies, and sometimes discounting is not applied at all.

The study of HEAL did not apply discounting rates to all cost estimates and mostly focused on the cost we are carrying now from exposure to EDCs in the past (current costs). This is in contrast with the studies of the Nordic Council and Trasande and co-authors, which assessed the effects of current

prenatal exposure to potential EDCs and the resulting health effects in the near and far future thereby applying discounting rates (future costs).

Type of costs modelled

One can distinguish between direct, indirect and intangible costs. Direct costs have been included in all studies, although it can vary what has been included as direct costs. It should be noted that indirect and intangible costs have not always been included in calculations, which results in large differences in actual costs. The composition of the costs is evaluated in more detail in paragraph 3.6.

Methodology to estimate the attribution of EDCs

To quantify the attribution of EDCs it is essential to set an estimate for the etiological fraction (the attributable fraction (AF) or the % of the cases with the disease that is attributed to EDCs). Two distinct methodologies are used; HEAL and the Nordic Council used fixed estimates (2/5% and 2/20/40% respectively) while Trasande and co-authors calculated EDC-attributable cost based on exposure-response relations (ERR) from epidemiological studies for specific compounds. The use of calculations make the AF based on stronger evidence compared to the more generic estimates of etiological fractions for EDC-attribution by HEAL and the Nordic Council. Unfortunately, this approach using ERRs cannot be applied for all health effects and all compounds. Qualitatively good epidemiological studies are not available for all of the health effects and suspected EDCs. To guarantee adequate results, suitable studies are needed that apply to a relevant population and exposure level, are corrected for confounders and consider potential selection bias. Therefore, it is crucial to mention the underlying epidemiological data used for the assessment of an EDC-attributable factor from an ERR.

Etiological fractions from the Nordic Council are based on expert judgement from experts in the field of male reproductive health. HEAL used the hypothetical 2-5% range as a conservative estimate for all health effects (also referring to one pioneering study linking one EDC (BPA) to 1,8% of obesity cases). As an advantage, these fixed fractions are estimated for the general impact of ED-effects combined, compared to one EDC only using ERRs. All scientist acknowledge that the exact contribution of EDCs to the total disease burden is unknown, as are other contributing genetic, lifestyle and environmental factors.

Strength of evidence and probability of causation

Trasande and co-authors considered the strength of experimental (toxicological) and epidemiological evidence according to predefined criteria and defined one probability of causation percentage range for these two types of evidence combined. As a framework for evaluation of EDCs is not available (see also paragraph 2.3), they adapted their approach after IPCC criteria that are used to evaluate strength of evidence for climate change. As such, the EDC-attributable cost estimates presented in the publications of Trasande and co-authors (Bellanger et al., 2015; Hauser et al., 2015; Legler et al., 2015; Trasande et al., 2015) were accompanied by a probability estimate that combined a rating of toxicological and epidemiological evidence (Trasande et al., 2015). The rating is provided for exposure-response relationships between the health effect and a specific chemical only and not for the overall strength of evidence for a role of EDCs in a specific health effect.

The strength of evidence of the exposure-response relations has been taken into account in the modelling of the overall estimate (Trasande et al., 2015). Recognizing the EDC-attributable cost estimates were accompanied by a probability arising from the combined rating of toxicological and

epidemiological evidence, a series of Monte Carlo simulations was performed to produce ranges of probable cost across all of the exposure-outcome relationships. This resulted in a best estimate, taken into account the different degrees of certainty. Across 1000 simulations, a median estimate of € 157 billion (annually for EU28) was derived (with a 90% C.I. between € 32 and 212 billion). A more detailed description of this methodology is given in the original articles (Trasande et al., 2015).

The studies of HEAL and the Nordic Council did not apply such an approach to correct for evidence of causation.

3.5. Comparison of total cost of EDC-associated health effects

An overview of the different EDC-attributable socio-economic cost estimates per health effect is provided in Table 6. In the HEAL report and the publications from Trasande and co-authors, where multiple health effects were assessed, remarkably dominant contributors to the total costs were found (Table 5 and 6). These are neurobehavioral disorders, more specifically autism (and related disorders) in the HEAL report and loss of IQ points in the Trasande et al. study.

For some health effects, the socio-economic cost estimates are similar, which is noteworthy given the fact that different methodologies and input parameters were used to obtain these results. For instance, the estimation for cryptorchidism costs are very similar among the three studies. For male reduced fertility, however, the costs calculated by the studies of Trasande and co-authors are more than an order of magnitude higher compared to the results of HEAL and the Nordic Council. Similarly, Trasande's calculated cost of AD(H)D are much higher compared to the calculation of HEAL, while HEAL's calculation of autism is very high compared to Trasande's estimate. Possible causes of these differences in estimated socio-economic cost for different health-effects will be further explained in section 3.6.

3.6. Detailed evaluation of EDC-associated cost per disease

Per disease, the underlying cost-of disease studies, calculations, data on number of cases of disease (incidence/prevalence) and adjustments of cost were evaluated. Detailed results on the evaluated parameters (as listed in Table 5) are provided in **Annex B**. This section describes the main differences and similarities between the socio-economic cost estimates. We aim to increase the understanding in (dis)similarities in costs estimates and enhance interpretation of results.

3.6.1. Reduced fertility

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

Male vs. female reduced fertility and associated ART-type

The reports of the Nordic Council (Olsson et al., 2014) and the group of Trasande (Hauser et al., 2015) focused on reduced male fertility only, while the report of HEAL (HEAL, 2014) also included decreased female fertility. The Nordic Council estimate is based on therapeutic costs and lost working hours for the so-called "ICSI treatment" only. ICSI (intracytoplasmic sperm injection) is a fertility treatment where one healthy sperm is selected and injected directly to an egg for fertilization (IVF) *in vitro*. As such, it can bypass male infertility caused by a decline in quality and quantity of sperm. However, it is often argued that the exact cause for infertility or subfertility of a couple is unclear and might also be attributable to female infertility. As such, other forms of assisted reproductive technology (ART) can be applied to treat infertility. HEAL included all forms of ART and presented a combined impact assessment of male and female infertility problems. While female

fertility is not the (main) scope of the Hauser study, a cost estimation for all kinds of ART treatments (thus including treatments to overcome female fertility) was included. Other forms of ART (including other forms of IVF) have a higher average cost compared to ICSI (Olssen et al., 2014). As a result, the estimate by the Nordic Council based on ICSI only could be either an over- or underestimate of male infertility.

Table 6. EDC-attributable cost per health effect and total EDC-attributable annual socio-economic cost the EU (in billion €) as described by the Nordic Council, HEAL and Trasande *et al.*.

Source	Nordic Council			HEAL		Trasande *et al.*		
Etiological fraction / type of estimate	**2%**	**20%**	**40%**	**Total (2%)**	**Total (5%)**	**low**	**base case**	**high**
Reproductive tract and fertility								
Reduced female fertility				0,048 - 0,062	0,120 - 0,155			
Reduced male fertility	0,007	0,072	0,145			4,71	4,71	4,71
Cryptorchidism	0,018	0,181	0,363	0,018 - 0,026	0,045 - 0,065	0,117	0,130	0,130
Hypospadias	0,009	0,089	0,178					
Neurobehavioral diseases and disorders								
Autism spectrum disorders (ASD)				4,52	11,3	0,080	0,199	0,399
AD(H)D				0,014	0,035	2,62	4,14	4,93
IQ loss						4,22	133,4	183,6
Mental retardation						6,11	22,6	33,43
Hormone-related cancers								
Breast cancer				0,320	0,800			
Prostate cancer				0,180	0,450			
Testis (testicular germ cell) cancer	0,025	0,249	0,499			0,313	0,848	0,848
Metabolic syndromes, other								
Obesity child				1,62	4,05	1,56	1,56	1,63
Obesity adult						15,6	15,6	15,6
Diabetes mellitus (type 2)				6,0	15,0	1,44	1,44	17,2
Increment death rate among men						7,96	7,96	7,96
TOTAL	**0,059**	**0,591**	**1,185**	**12,7**	**31,6**	**44,7**	**192,6**	**270,4**
TOTAL after correction for probability of causation	**NA**	**NA**	**NA**	**NA**	**NA**	**157,0 (90% C.I. 32-212)**		

Note: Cells have been merged if they reflect cost estimates of combined health effects. For the studies of Trasande *et al.* the low and/or high estimates are provided as sensitivity analysis; if these low and/or high estimates were not calculated, the base case estimate (in grey) are taken as upper and lower boundary of total EDC-related healthcare cost.

Costs per case

The cost estimates for reduced fertility from HEAL (€ 4.470 - € 5.920 per treatment cycle) and Hauser et al. (€ 7.621 per infertile couple that seeks treatment) are somewhat higher compared to those of the Nordic Council (€ 3.480 per infertile male, regardless whether treatment is sought or not).

It should be noted that costs are hard to compare due to differences in scope of studies. The Nordic Council and Hauser et al. studies specified cost per infertile male. The estimate for infertility in the HEAL study based on average cost per IVF/ET (Embryo Transfer) treatment cycle, which is considerably more expensive than the cost per treatment cycle used by the Nordic Council and Hauser et al. studies. The cost per case in the HEAL study might actually be higher due to the fact

that the cost estimate is based on an older study from 1995 (when ART treatment were more uncommon). Another difference can be found in the infertile males included in the cost estimates. Not all males who are infertile seek treatment, hence will not use healthcare and therefore do not create societal cost. In its estimate, the Nordic Council study included all infertile males and calculated a weighted average cost including males that did not seek treatment as well as males who did seek treatment (with and without success – a live birth resulting from the treatment), thus dividing fertility treatment cost over all infertile males. Also, in contrast to the estimate of HEAL and Hauser et al., the estimates in the Nordic Council study were discounted to correct for the time lap between prenatal exposure to EDCs and the time fertility treatment is sought (see also paragraph 3.4). Therefore, the Nordic Council estimate (per case) is only half the cost estimate specified by Hauser et al. This is despite the fact that indirect non-healthcare costs (such as productivity losses) have been included in the Nordic Council estimate, while these have not been included in the cost in the estimate of Hauser et al. nor in the HEAL study.

Main drivers of total cost

An important driver for the total cost estimate for infertility is the amount of cases or treatment cycles used for calculations. The Nordic Council study used an incidence rate for male infertility of 4% for newborns. In the HEAL study, the total amount of ART cycles in 2009 was used for the total cost estimate, referring to a total number of ART cycles in the EU of about 500.000/year. The Nordic council report referred to 100.000 infertility cases in the EU per cohort of which part will undergo various ICSI treatments. Both studies applied an EDC-attributable factor, yielding a similar number of attributable cases or cycles of around 10.000. Depending on the specific EDC-attributable factor, the Nordic council report estimated ED-related male infertility cost between € 7 and 145 million and the HEAL study estimated the ED-related male and female infertility cost between € 48 and 155 million.
In contrast, in the paper of Hauser et al., the amount of infertile males due to phthalate exposure was estimated using the number of "EU women aged 20-44, living in consensual union, not using contraception" as a proxy for couples who want to become pregnant. This suggests that a lifetime timeframe of fertile years of a woman has (mistakenly) been used as an annual estimate for male infertility cases. Next, this number, 11.8 million women, was multiplied by 9.38% (the total infertility rate attributable to phthalate exposure) and 56% (the rate of couples who seek medical care for infertility), yielding 618.000 attributable cases. This result is almost two orders of magnitudes higher compared to the estimates in the other two studies. This explains the much higher cost estimate of € 4,71 billion for male fertility by Hauser et al. compared with the estimates of the studies of The Nordic Council and HEAL.

Summary

- Despite a different scope, cost per case or treatment cycle for infertility are within the same order of magnitude;
- Final estimates for ED-related infertility of the Nordic Council and HEAL are in the same range (resp. € 7 - 145 million, and € 48 - 155 million) in spite of the fact that different methodologies were used;
- The high number of estimated infertility cases in the Hauser et al. study (compared to the number of cases in the report of HEAL and the Nordic Council) explains the higher overall costs of € 4.71 billion. Therefore, the estimates of HEAL and the Nordic Council are considered more realistic.

3.6.2. Cryptorchidism

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

Cost per patient

Cryptorchidism or undescended testes is a birth defect where one or two testes are not in the scrotum at birth. If the testes do not descent spontaneously, it will be treated by a surgery called orchiopexy. One of the most important differences in the cost estimates for cryptorchidism in different studies is whether the indirect and intangible costs were included. The authors of the Nordic Council (Olsson et al., 2014) included all kinds of direct, indirect and intangible costs (see Annex B), while the authors of HEAL (HEAL, 2014) only used direct costs of surgery to calculate economic effects of cryptorchidism. In the paper of Hauser (Hauser et al., 2015), cost estimates were based on the calculations presented in the Nordic Council report, and hence also include direct, indirect and intangible costs.

The direct costs provided by the authors of the Nordic Council and HEAL are based on the Swedish patient registry and a US study, respectively. The US study differentiates between surgery performed soon after birth (€ 5715) and post pubertal surgery (€ 8415). In the Nordic Council report it is argued that development of cryptorchidism in later life is rare, and not relevant for EDC-related illness because its development depends on other factors than hormones. Thus, an average surgery cost per child is obtained (€ 4429). This estimate is lower compared to the HEAL-estimate, however the difference is less than a factor of two.

In the Nordic Council report, lost working hours of parents are added (€ 1000), as well as intangible cost. Especially the intangible costs are large with an estimated cost of € 29.200, based upon a discounted loss of 0,42 QALY (a measure of loss of quality of life). One QALY is valued at € 70.200, which leads to high intangible cost. The intangible cost makes up the major part of the costs associated with cryptorchidism in the Nordic Council report and Hauser study, and explains the large difference between the total cost estimates per patient in different studies.

Incidence and EDC-attributable factor

There is a large difference in incidence of cryptorchidism used for calculations by the Nordic Council and HEAL. The Nordic Council authors reason that a large part of the cases detected at birth will resolve spontaneously, and therefore requires no treatment. Only one out of five cases is assumed to be treated by surgery, which leads to an overall 1% of the total number of male births that require surgical treatment for cryptorchidism. In contrast, the HEAL study uses an incidence rate of 6%, but assumes for its calculations that all cases require surgery, either soon after birth or after puberty. In a footnote, however, it is stated that the incidence should actually be 3% given the fact that by three months of age the incidence is usually more than halved because of natural, spontaneous descend. Yet, the latter aspect is not used for further calculations, thus creating an incidence that is six times higher compared to the Nordic Council and the Hauser et al. studies.

For the amount of EDC-attributable cases, the HEAL report uses 2% and 5% of the total incidence in the EU. This is considerably lower than the Nordic Council study that uses 2%, 20% and 40% as EDC-attributable factors and Hauser et al. who use 8,9%, calculated based on exposure-response relationships.

Total costs

Despite important differences in the types of costs included and the incidence of cryptorchidism taken for calculations, the final cost estimates are remarkably similar. The use of higher costs per patient in the calculations of the Nordic Council and Hauser et al., do not lead to higher estimates compared to the HEAL calculations, because a lower incidence rate for surgery is used in the latter study. Similarly, the higher incidence for surgery used by the authors of HEAL (not correcting for cases that resolve naturally) does not lead to higher total cost because cost per patients are smaller, and a lower attributable fraction for the relation between EDCs and cryptorchidism is used.

Summary

- Despite differences in cost input parameters and incidence use, total cost are noticeable similar;
- Intangible cost, taken into account in the study of the Nordic Council, have a large contribution to the total cost per patient;
- The HEAL study does not correct for cases that resolve naturally, and therefore uses an incidence of 6% compared to 1% by the Nordic Council and Hauser et al. studies;
- The total cost estimates for EDC-attributable cryptorchidism are in the same order of magnitude with € 18 million and € 363 million (The Nordic Council), € 117 – 130 million (Hauser et al.) and €18 – 65 million (HEAL).

3.6.3. Hypospadias

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

Hypospadias is a male birth defect in which the opening of the urethra is on the underside of the penis. Treatment requires surgical repair shortly after birth. Although the HEAL study (HEAL, 2014) suggests that both hypospadias and cryptorchidism are quantified, in fact only costs of cryptorchidism are estimated. Trasande et al. do not address EDC-related costs for hypospadias. Consequently, only the Nordic Council study (Olsson et al., 2014) provides a cost estimate for hypospadias. It is reported that costs are mainly medical cost, however there are also some potential costs for sick leave of the parents, as well as costs related to secondary effects of hypospadias.

Intangible cost

The study of the Nordic Council includes direct, indirect and intangible costs. A total cost per case of €39.616 is presented. Especially the intangible cost (0,4 QALY with a cost of € 28.080) makes up a large part of the total costs (71%) when compared to direct costs (26%) and indirect costs (3%). Direct costs are relatively straightforward, and include a surgery to correct the abnormally located urethra opening of newborn boys. This calculation also includes treatment for secondary effects of hypospadias (urethrocutaneous fistula and urethra stricture). If surgery is successful, these boys should have little or no loss in quality of life due to possible psychosexual impairment. As a result the authors argue that the discounted QALY value of 0,40, reflecting the intangible cost, should be considered as a high estimate.

With EDC-attributable fractions of 2%, 20% and 40%, total cost in the EU for hypospadias are € 9 million, € 89 million and € 178 million per year, respectively.

3.6.4. Autism spectrum disorder, (ASD)

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

Autism spectrum disorder (ASD) is a neurological and developmental disorder that begins early in childhood and lasts throughout a person's life. It affects how a person acts and interacts with others, communicates and learns. It includes what used to be known as Asperger syndrome and pervasive developmental disorders (U.S. National Library of Medicine, 2015).

Costs per case per annum

EDC-attributable autism costs were quantified in the HEAL study (HEAL, 2014) and Trasande studies (Bellanger et al., 2015). Both use studies in which autism costs for the UK were estimated. Besides cost studies from the US, there are no other cost of autism studies available. Due to a higher living standard in the UK compared to other EU countries, there is a risk for overestimation of cost when extrapolating these cost to other EU countries.

The study on costs of autism used in the HEAL study is 5 years older, *i.c.* (Knapp, Romeo, & Beecham, 2009) compared to that of Bellanger et al. *i.c.* (Buescher, Cidav, Knapp, & Mandell, 2014). Both studies include direct and indirect cost, e.g. accommodation costs, medical treatment and care, special education, productivity loss from parents and individuals with ASD, voluntary organization help, welfare benefits and family expenses. The quantification distinguishes between individuals with and without intellectual disability (ID) and is also disaggregated for different age classes. In addition, Knapp et al. (2009) also showed different estimations according to place of residence (e.g. living at home, supported homes, or hospitals).

Costs per annum per case of autism are in a similar range: Knapp et al. calculates a total cost range for UK adults between £32.681 per annum (no ID; living in private household) and £97.863 (with ID, living in a special accommodation or hospital). Buescher et al. (2014) quantify total cost for UK adults between £47.947 (without ID) and £ 86.099 (with ID). Knapp et al. (2009) provide a wider range of cost per annum because the study specifies the large difference in costs between individuals who live in a private home, and those individuals who live in a supported accommodation, while Buescher et al. includes only an average cost per individual for accommodation and residential care.

Lifetime cost and EDC-attributable costs

In both studies, lifetime costs have been estimated. The lifetime costs provided by Buescher et al (2009) have been discounted with a rate of 3,5% per year, which results in an estimate of £ 0,92 million (no ID) to £ 1,5 million (with ID). In contrast, the lifetime estimate of Knapp et al (2014) is not discounted and therefore much higher with £ 2,9 million (no ID) to £ 4,7 million (with ID).

Bellanger et al. (2015) used this discounted lifetime estimates to calculate an EU-average lifetime cost of € 630.000 per individual with autism. An EDC-attributable fraction of 8,88% was calculated, but finally a value from literature was used (2-10%), further reduced to 0,97%, 2,425% and 4,85% to correct for double counting coexisting IDs. These fractions were applied to the total number of 8-year old children diagnosed with autism (0,62% of the total population of 8 year olds). Accordingly, these data should be interpreted as "current exposure to this cohort (one year) will lead to a socio-economic loss between € 80 million and 400 million in the future".

The HEAL study did not use the lifetime estimate for its calculations, but used the total annual socio-economic cost burden for autism spectrum disorders in the UK, which was calculated by Knapp et al. (2014) to be € 28,4 billion for adults, at present. This amount is based on an assumed prevalence of ASD of 1%. The UK societal cost were extrapolated to the population size of the EU28, leading to

present annual cost of € 226 billion. If the EDC-attributable factors of 2% and 5% from the HEAL study are used, this will yield a result of € 4,52 billion - € 11,3 billion annually. This estimate should therefore be interpreted as "annual costs that could potentially be attributed *now* to EDC-exposure from the past". The use of undiscounted values is a main driver for the difference seen with the calculation of Bellanger et al. The use of higher prevalence rates for ASD and use of costs based on UK living standards, which are higher than the EU average, provide additional explanation to the difference between the results.

Clarifications for high lifetime costs for ASD

In general, costs per individual per annum and generated lifetime cost for ASD are very high as is shown by the two independent studies evaluated above. These high costs can be explained by the fact that autism is a complex pervasive mental disorder, which lasts throughout a person's lifetime and requires lifelong support. It should be noted, however, that cost-of-disease studies using a bottom-up approach (calculating cost per individual and extrapolating this to the whole population) tend to overestimate the burden of societal costs (as seen in top-down cost studies, where actual healthcare expenditures are analyzed and broken down to cost per patient).

Summary

- Lifetime costs for individuals with ASD are high, especially because of life-long institutional and residential care are needed;
- Bellanger et al. estimated a cost of € 80 – 400 million for EDC-related ASD, while the estimate of HEAL is at least one order of magnitude higher with annual cost in the EU28 of € 4,52 billion - € 11,3 billion;
- Main driver for the difference in the final cost estimate seems to be the use of discounted lifetime cost (future costs due to current EDC exposure) versus non-discounted lifetime costs (current costs due to historical EDC exposure).

3.6.5. Attention Deficit (Hyperactivity) Disorder, AD(H)D

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

Attention Deficit (Hyperactivity) Disorder (AD(H)D) are characterized by problems with attention, impulsivity and (in case of ADHD) hyperactivity. Childhood AD(H)D is likely to persist into adulthood and may constitute a lifelong impairment.

Costs per case and costs per annum

The costs for EDC-attributable AD(H)D were calculated in the HEAL study (HEAL, 2014) and Bellanger et al. (Bellanger et al., 2015). The HEAL report based its calculation on the cost-of-disease study of Schlander (Schlander, 2007). Bellanger et al. made two calculations for EDC-suspected substances, one for OPs-attributable cost, and one for PBDE-attributable cost. Both calculations are based on a recent cost study of Le and co-authors (Le et al., 2014).

There are large differences between these cost studies. The study of Schlander only provides the cost for AD(H)D medication, which was estimated to be € 56,07 per person per year. In contrast, the study from Le et al., used various direct and indirect costs derived from a review of seven scientific papers to estimate the annual cost per individual with AD(H)D. This inclusion of direct cost other than medication and indirect costs resulted in a much higher estimate, between € 9.860 and € 14.483 per person with AD(H)D on an annual basis. Bellanger et al. adapted the cost per annum to a ten-year

long discounted and EU-wide, estimate per case. This resulted in a total cost of € 77.000 per individual.

Prevalence and EDC-attributable factor

A prevalence rate of 6,1 % and an EDC-attributable factor of 10,76 % - 17,28 % for OPs and 12,53 % for PBDE was applied by Bellanger et al.. For the two chemicals combined, this resulted in an estimate between € 2,62 and € 4,93 billion annual cost for the EU28.

The study of Schlander et al., used a prevalence of 3,9% based on diagnosis among UK children and adolescents from which 2,54% use medication. Total cost of medications for ADHD in the UK in 2005 was € 91 million (children and adolescents). If this extrapolated to EU28 situation and used with an attributable factor of 2% and 5% for EDCs by HEAL, this results in an estimate of € 14 – 35 million. This is only a fraction of the cost calculated by Bellanger and co-authors (approx. 20 times lower), mainly because it does not include substantial other costs related to AD(H)D.

Summary

- The large difference between the cost estimates for ADHD caused by EDCs is mostly explained by the scope of the underlying cost studies (various direct and indirect costs *vs.* cost for medication only).
- In addition, Bellanger and co-authors have used a much higher EDC-attributable factor than HEAL.
- Taken together the overall differences between both studies it may be concluded that the cost estimations of ADHD in the EU28 by Bellanger et al. appear to be more realistic, although the used prevalence rate is rather high.

3.6.6. IQ loss

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

IQ loss calculations in the EU

The health and economic impacts of EDCs on IQ loss were quantified by Trasande and co-authors and presented in the paper of Bellanger (Bellanger et al., 2015) for two groups of compounds: PBDEs and OPs. Previously a similar quantification was performed of PBDE- and OPs-related IQ loss in the Netherlands (Rijk & van den Berg, 2015). The latter report was not published in peer-reviewed literature, but is available online (Rijk & van den Berg, 2015). This estimate is used here for comparison.

For both PBDE and OPs, exposure-response relationships (ERR) are only available from epidemiological studies in the US. So far, European epidemiological studies have not revealed such effects. The US ERRs were used to calculate the loss of IQ in Europe. It should be noted that overall levels of PBDEs in the EU are significantly lower than in the US due to less stringent fire regulations and less use of PBDEs in the EU. This might lead to uncertainty for estimation of European IQ loss in the lower exposure regions when using high US PBDE exposure data. In contrast, OPs exposure is at a similar or higher levels than the US.

In the paper of Bellanger et al., the impact of PBDEs on IQ was modelled using an earlier ERR for BDE-47 in cord blood (Herbstman et al., 2010) in the base case scenario, and for sensitivity analysis (high case scenario) BDE-47 in maternal serum (Eskenazi et al., 2013). PBDE exposure levels were based on

various studies. For the study of Rijk & van den Berg, there appeared to be insufficient data on BDE-47 in cord blood in the Netherlands. Instead, BDE-47 exposure levels in maternal serum are available (Meijer et al., 2008), which are lower than the reference levels used by Bellanger et al. The Dutch levels were applied to the ERR from Chen (Chen et al., 2014), as this ERR also holds at lower exposure levels (compared to higher US PBDE levels). In the study of Bellanger et al., PBDE-associated loss per newborn was estimated to be up to 1,94 IQ points, depending on exposure level and scenario. IQ loss was only expected in the highest exposure groups (75 and 90 percentile exposures). This is similar to results for the Netherlands estimated by Rijk & van den Berg, were in the 95 percentile group a loss of 0,96 IQ points per newborn was expected (but in a smaller part of the population).

For OPs, Bellanger et al. used two ERRs based on total urinary dialkylphosphate (DAP, OP metabolites) as a low case (Engel et al., 2011), and a high case (Bouchard et al., 2011). Furthermore, the weighted average from these two studies was used as a base case estimate. In the Dutch study, an ERR was used from the study of Bouchard only, as this ERR is based on exposure levels comparable to the relatively high OP exposure levels observed in the Netherlands (Ye et al., 2009). With 0 - 7,01 IQ points, the OP-associated IQ loss was significantly higher than for PBDEs (Bellanger et al., 2015). For the Netherlands, a smaller loss of 1,69 to 5,12 IQ points per newborn was calculated (Rijk & van den Berg, 2015). One crucial difference is that in the Dutch study, loss of IQ was calculated relatively to the median exposure level in the US, to correct for differences in exposure levels and related responses between the Netherlands and the US. In the study of Bellanger et al., also effects at lower exposure levels were calculated.

Value of IQ points

The only available approach to value IQ loss is based on the lifetime economic productivity loss per IQ point, is based on US studies. There are no directs costs (such as healthcare costs) quantified, and cost therefore do not represent actual expenditures. The comparison with the US might not be one-to-one applicable to the EU, as there is more heterogeneity in income in the US, however no European approaches are available.

The loss of one IQ point has been related to a 2% decrement in lifetime economic productivity (1.76-2.39% sensitivity analysis). This value of 2% (US EPA, 1997) consists of a direct effect of IQ on wage of 0.5%, combined with two indirect effects, namely 1.0% for less schooling and 0.477% for reduced labor force participation (Ashenfelter & Ham, 1979; Krupnick et al., 1989; Needleman, Schell, Bellinger, Leviton, & Allred, 1990).

Similar to earlier studies, Bellanger et al. valued one IQ point at $ 19.269, which is discounted and adjusted for historical changes in the Consumer Price Index. This was further adjusted to country-specific purchasing power parity (PPP) adjusted per capita gross domestic product (GDP). This resulted in an average value of € 9.600 lifetime loss per IQ point. In the Dutch study, the best estimate for 2% loss of lifetime earnings in the Netherlands corresponded to a (not discounted) value of € 12.120 (Rijk & van den Berg, 2015).

Socio-economic impact of IQ loss

According to these calculations, billions of IQ points have been or will be lost in newborns that are exposed to PBDEs and OPs. Bellanger et al. estimated the loss of 873 000 (149 000 – 2,02 million) IQ points due to exposure to PBDEs, and the loss of 13,0 million (4,24 – 17,1 million) IQ points due to OP exposure. This leads to cost estimates for the EU28 are in a range of € 1,43 – 19,4 billion for PBDEs

and € 40,8 – 164 billion for OPs, annually. Similarly, annual cost in the Netherlands were estimated to be € 100 million (€ 2 – 196 million) due to PBDE exposure (Rijk & van den Berg, 2015). When this is extrapolated to EU28 based on population only, this would be a total of cost of € 3 billion (€ 60 million – 5,9 billion) on the basis of 248 000 IQ points lost (5500 – 484 000). For OPs, Dutch estimates were € 2,7 billion (€ 1,1 - 4,4 billion) annually (Rijk & van den Berg, 2015). This would correspond to annual cost of € 81,3 billion (€ 31,9 – 130,1 billion) for EU28, based on 6,7 million IQ points lost (2,6 – 10,8 million). It should be noted that in the extrapolation from cost in the Netherlands towards EU28 costs, no correction factors for GDP-PPP were applied.

The socio-economic impacts of IQ loss are entirely based on indirect effects. Costs do not include direct costs (actual expenditures). Nonetheless, these estimates indicate that EDCs can have a large socio-economic impact on society via IQ loss.

Other trends in IQ

It is not clear how the EDC-attributable loss of IQ contribute with other trends that are seen for IQ. For example, some studies have reported an increase in IQ over the last decades (Mingroni, 2007). It could be argued that a definition of "foregone" IQ points would be better applicable instead of IQ points lost. As a result, a different methodology (e.g. Willingness To Pay (WTP)) to value socio-economic costs of EDCs might be needed in order to provide an estimate that takes into account the *reduced increase* in IQ.

Summary

- IQ loss has been quantified for the EU in the paper of Bellanger et al. and for the Netherlands by Rijk & van den Berg;
- Based on different, but comparable ERRs and exposure levels, both studies showed that best estimate for annual PBDE- and OPs- related IQ loss in the EU is expected of 248 000 – 873 000 IQ points for PBDE and 6,7 million – 13 million for OPs;
- IQ points are valued using US EPA approaches, calculating indirect costs only (lost lifetime economic productivity);
- Annual economic losses in the EU are estimated to be between € 60 million and € 19,4 billion for PBDE, and between € 32 billion and € 164 billion for OPs.

3.6.7. Mental retardation

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

EDC-attributable cost for mental retardation

The economic loss for EDC-attributable mental retardation (also called intellectual disability - ID) is calculated using the same exposure-response relationships for PBDE- and OPs-related IQ as described above for IQ loss, and presented in the paper of Bellanger (Bellanger et al., 2015) in the series of Trasande and co-authors. However, there is no overlap in cost estimates for IQ loss (as described in 3.6.6) and mental retardation. No other reports are available that estimate the socio-economic effect of EDCs via mental retardation.

The EDC-attributable cases of mental retardation are based on an increase in number of individuals that can be classified as mentally retarded (IQ < 70) if the whole IQ distribution curve shifts several points to the left (lower side) due to an EDC-related decrease in IQ. Using this approach, it was modelled that 3290 (544-8080) extra cases of mental retardation would be attributable to PBDE. For OPs, 59.300 (16.500-84.400) extra cases of mental retardation were estimated. This approach

assumes a normal distribution for IQ in the population and an equal effect of EDCs among all IQ levels. And similar to IQ loss calculations, an increasing trend in overall IQ is not taken into account here.

Direct costs for mental retardation per individual
The total average cost of an individual with intellectual disability in EU28 is estimated to be € 360.000 (discounted lifetime cost per capita, assuming a mean life span of 50 years). This estimate is calculated from annual direct costs of € 10.334 per individual based on several EU studies (Gustavsson et al., 2011; Olesen, Gustavsson, Svensson, Wittchen, & Jönsson, 2012; Polder, Meerding, Bonneux, & Van Der Maas, 2002). In contrast to the value of IQ points, the annual cost of an individual with ID includes a wide range of direct cost (healthcare and non-healthcare), e.g. pharmaceutical care, hospital care, institutions, activities, nursing/home care, and administration. However, while only direct cost estimates are available, it is recognized that indirect costs (e.g. income and productivity losses) are also substantial. Bellanger et al. has also calculated indirect cost as income loss due to lost IQ points (paragraph 3.6.6). Again, there is no overlap in cost estimates of IQ loss and mental retardation; in fact the costs are additive. Furthermore, there is also no overlap with costs of ASD, as the calculations for ASD have been adjusted for double counting by coexisting ID among individuals with ASD.

Cost for mental retardation in the EU related to PBDEs and OPs
Total aggregated cost for PBDE- and OPs-related intellectual disability were estimated by Bellanger et al. to be between € 6,1 and 33,4 billion (average of € 22,6 billion). If these costs are compared to cost estimates of ID based on actual attributable expenditures within healthcare budgets, it was clear that indeed the costs for ID are high and make up 9% of national health care budgets in the Netherlands (Polder et al., 2002). In 2010, total cost for ID in the EU were found € 43,3 billion (Gustavsson et al., 2011).

Summary
- Intellectual disability (ID) has been quantified for the EU in the paper of Bellanger et al. only, assuming a shift in IQ curve of the general population due to PBDE- and OPs related IQ loss;
- It is calculated that 17 000 – 92 000 extra cases of ID are expected, with aggregated costs of between € 6,1 and 33,4 billion (average of € 22,6 billion) for the EU per year;
- Only direct costs are included in the estimate, therefore there is a risk that these costs are an underestimate of real socio-economic costs of this effect.

3.6.8. Breast cancer

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

Socio-economic loss due to EDC-attributable breast cancer, as well as prostate cancer, was calculated by the authors of the HEAL study only (HEAL, 2014). It was based on calculations of a recent EU-wide study (EU27) that estimated societal costs of four common cancers (breast, prostate, lung and colorectal cancer) (Luengo-Fernandez, Leal, Gray, & Sullivan, 2013). In this study, direct healthcare costs and indirect productivity losses from patients and caregivers were generated for each specific country, as well as average costs for EU27 as a whole. The HEAL study included only minor adjustments with respect to the extrapolation to EU28 (including Croatia) and an adjustment of the costs from 2009 to 2012.

The annual economic cost in EU28 due to breast cancer was estimated € 16 billion. The HEAL study set an EDC-attributable fraction of 2% and 5% for breast cancer, which amounts to an annual EDC-attributable cost estimate of € 320 to 800 million.

3.6.9. Prostate cancer

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

Similar to the calculation of the EDC-attributable costs for breast cancer, the HEAL report (HEAL, 2014) presented a calculation of EDC-attributable cost of prostate cancer using the study of Luengo-Fernandez et al. (Luengo-Fernandez et al., 2013). This study calculated annual economic cost in EU27 due to prostate cancer to be as € 9,04 billion, which is about half of the cost calculated for breast cancer. This difference can be explained (at least partially) by higher productivity losses due to morbidity and mortality for breast cancer, compared to prostate cancer. When using again an EDC-attributable fraction of 2% and 5%, the annual EDC-attributable cost estimate would be in the range of € 180 to 450 million for prostate cancer.

The use of a recent, EU-wide paper on direct and indirect cancer costs certainly increases the strength of the cost estimate for breast and prostate cancer.

3.6.10. Testicular cancer

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

The EDC-related costs of testicular cancer were provided in the studies by the Nordic Council (Olsson et al., 2014) and in the paper of Hauser *et al.* (Hauser et al., 2015). The costs of testicular cancer used in the publication of Hauser et al. were largely based on those calculated by the Nordic Council. However, total annual costs for EU28 attributed to EDCs are substantially different: The Nordic Council report estimates a range of € 25 – 499 million, whereas Hauser and co-authors calculates a range of € 313 – 848 million.

Cost calculations

The authors of the Nordic Council report used data from Swedish patient registers, which were further extrapolated to the EU28 situation. It should be noted that these costs might not reflect cost levels in other EU countries. Also direct healthcare (surgery and care), productivity loss, and intangible cost were included in the cost estimate of the Nordic Council. All costs were discounted for 35 years, which is the average age at which testicular cancer occurs. Especially the intangible costs are high, with a discounted value of 1,09 QALY valued at € 76.740 in total. This makes up over 90% of the total lifetime cost per case of testicular cancer. Total cost per case was € 80.980.

Although Hauser et al. (2015) based their calculations on the Nordic Council study, the cost estimate per case is with approximately € 124.000 per case 50% higher than in the Nordic Council study. The exact cause to this difference is unknown. Some adjustments have been performed in the study of Hauser et al., e.g. country-specific GDP and medical cost inflation. However, this cannot entirely explain the difference between both studies. Another contributing factor might be that non-discounted QALYs have been used to estimate intangible cost in the Hauser et al. study.

EDC-attributable fraction

Hauser et al. (2015) calculated the EDC-attributable fraction (AF) to be 35,5% in its base case scenario, and 13% in its low case scenario). The base case AF was calculated using PBDE

concentrations from one study only, which was considered to be representative for the EU population. The EDC-AF at lower exposure levels was calculated combining PBDE concentrations from nine studies. Despite the different approaches, the calculated EDC-attributable fraction of Hauser et al. is similar to the generically chosen mid- and high estimate of 20% and 40% by the Nordic Council.

Summary

- There is a difference between cost estimates of the Nordic Council (range of € 25 – 499 million) and Hauser and co-authors (€ 313 – 848 million), while the estimate of Hauser et al. is based upon the Nordic Council study. The exact explanation is not known;
- The estimates include a large part of intangible costs (90%);
- Attributable fractions based on calculation using ERRs (13% and 35,5%) are similar to those based on estimations from the Nordic Council (2%, 20% and 40%).

3.6.11. Obesity

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

EDC-attributable cost for obesity was quantified in the studies by HEAL (HEAL, 2014) and Trasande and co-authors as presented in the paper of Legler et al. (Legler et al., 2015).

Calculation of costs by HEAL

The calculation in the HEAL study is based on a European Commission working paper on nutrition, overweight and obesity in which it was estimated that costs for obesity would be 0,3% of the GDP (in 2005). This includes direct healthcare cost and productivity loss from morbidity and mortality (European Commission, 2007). For including overweight, this figure could be doubled. Applying this percentage to EU25 and using the 2005 GDP, yields a cost estimate of € 81 billion for obesity and overweight combined. The HEAL study proposed an EDC-attributable fraction of 2% and 5%, which results in a cost range of € 1,62 billion – 4,05 billion for obesity and overweight. This amount could be an underestimation for various reasons, e.g. these costs were not further adjusted to the EU28 situation and present GDP. In addition, the costs of overweight and obesity for children were not taken into account in the EC report. Cost of lower wages, psychiatric disorders (e.g. depression) and intangible costs are recognized in this reports as contributing factors, but were not taken into account., It should also be noted that it is uncertain exactly what kind of obesity-attributed health effects were taken into account. Part of the overweight costs were addressed to diabetes in the EC report, while HEAL assumed that these costs are separate and additive.

Calculation of costs by Legler et al.

The approach followed by Legler and co-authors to calculate EDC-related costs for obesity is more complex and requires further evaluation. Three situations are modelled: DDE-attributable child obesity (based on an exposure-response relationship for children at the age 10 (Iszatt et al., 2015)), BPA-attributable child obesity (for children at age 4 (Valvi et al., 2013)), and phthalate-attributable adult female obesity (relation only found for females, not for males (Song et al., 2014)). The three situations use different cost studies and adjustments.

The cost estimate for child obesity is based on a recent meta-analysis (Finkelstein, Graham, & Malhotra, 2014), which provides an estimate of incremental direct medical cost during the lifetime of an obese child relative to a normal-weight child, who maintains normal weight throughout adulthood. Indirect or nonmedical costs (e.g. productivity loss), and health-related quality of life

were not included in this meta-analysis by Finkelstein et al.. For DDE-attributable child obesity starting at age 10, direct medical incremental lifetime costs were € 15.820 per person (after adjustments by Legler et al. for currency and PPP per capita-GDP). Using the same source study (Finkelstein et al., 2014), BPA-attributable child obesity costs were estimated to be € 66.500 per person. Because this was originally a cost estimate for obesity acquired at the age of 4, Legler and co-authors added additional years and costs that added up to a total of € 48.500 per child. Despite the citation of four papers, it is not clear from the study of Legler et al. how and what type of costs were added to account for additional obesity cost between age 4 and 10. Still, it is a substantial addition to the original cost as specified by Finkelstein, especially considering that annual obesity-related costs have been shown to start small and increase with age (Finkelstein et al., 2014). Furthermore, for DDE- and BPA attributable child obesity, different chemical-specific ORs and age-specific obesity prevalence were used. A lower EDC-attributable factor was used for DDE-related child obesity at the age of 10, which leads to a substantial difference in the cost estimates. As a result, the costs of obesity for DDE were estimated between € 24,6 and 86,4 million, while those for BPA were estimated € 1,54 billion.

To determine the cost of phthalate-attributable obesity for adult women two studies were used to provide estimates on the total annual cost by direct health care cost (Cawley & Meyerhoefer, 2012) and intangible cost (Muennig, Lubetkin, Jia, & Franks, 2006). The direct healthcare cost (medical expenditures) were compared to those of a biological, non-obese, relative (Cawley & Meyerhoefer, 2012). Annual costs were aggregated over 15 years and discounted by 3% to produce an average lifetime estimate for additive medical expenditures of € 21.500 per person. In addition, it was found that obese women lived 7,2 QALYs less (Muennig et al., 2006). These QALYs were incorrectly mentioned in the Legler paper as DALYs. Legler valued one DALY (QALY) at $ 50.000. Although the interpretation and use of a DALY (reduction in "healthy" years) is different from a QALY (gain of years living in good quality of life) cost estimates for DALYs and QALYs are comparable. Therefore, this confusion does not have an effect on the final cost estimate. Also, ten years of discounting was applied to the QALYs, resulting in the total lifetime (intangible) cost of € 268.000 per female.

There is a large difference in the obesity cost estimate per person in the above three exposure scenarios, which is caused by the different scope of the cost studies and the age of disease onset. By taking QALYs into account, the cost estimate for phthalate-attributable female adult obesity is with € 15,6 billion much higher compared to DDE- and BPA-attributable childhood obesity (1,56 billion).

Summary

- The cost estimate per capita for phthalate-attributable female adult obesity is € 15,6 billion while DDE- and BPA-attributable childhood obesity combined lead to annual costs in the EU of 1,56 billion;
- Calculations for EDC-related female adult obesity includes a large part (over 90%) of intangible costs, therefore total costs for adult obesity are higher compared to childhood obesity which includes only direct medical costs.

3.6.12. Diabetes type 2

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

Both the HEAL study (HEAL, 2014) and Trasande studies (Legler et al., 2015) combined in their estimations on the costs of diabetes type 1 and 2. Per case, the economic burden of diabetes is

greater for type 1 than for type 2, and the difference increases with age (Dall et al., 2009). In total, the prevalence of type 2 is significantly greater than the prevalence of type 1, so type 2 is responsible for most of the economic burden of diabetes (91,4%) (Dall et al., 2009).

Annual cost and lifetime cost

The HEAL study based its estimate on a survey and study on direct healthcare and indirect non-healthcare costs of diabetes in five EU countries (Spain, UK, Germany, France and Italy) (Kanavos, van den Aardweg, & Schurer, 2012). The total cost for these countries is then extrapolated to EU28 based on population size, leading to an estimate of € 300 billion. The HEAL study estimates EDC attributable costs between € 6 and € 15 billion annually, with EDC-contributable factors of respectively 2 and 5%. As a result, the annual cost per person, using an EU prevalence of 6% (30 million individuals with an age between 20 and 79) would be € 10.000.

Legler and co-authors estimated the costs for diabetes based on the results of a worldwide study on diabetes in 193 countries (Zhang et al., 2014). Although the methodology and type of costs that were included varied between countries, it can be expected that these costs mainly represent direct healthcare expenditures (as it based on a top-down approach). The average annual cost per person in the EU was calculated to be $ 1927 (in International Dollars), which is considerably less than the annual cost of € 10.000 calculated in the HEAL study. Legler and co-authors converted this annual amount to Euros and lifetime cost (15 years with a discount rate of 3%) to € 29.600 per person.

EDC-attributable fraction

Next, in the HEAL study, EDC-attributable fraction was derived from two specific EDCs - DDE and phthalates – for which there are epidemiological studies available (Sun et al., 2014; Wu et al., 2013). The subsequent cost estimates in this study are for both compounds less than one billion Euro in the base case exposure scenario (together € 1,44 billion), which is much lower compared to the total estimates of the HEAL study (€ 6 – 15 billion).

In the publication of Legler and co-authors 20.500 phthalate-attributable cases of diabetes were estimated, which amounts in a total annual socio-economic cost burden of € 607 million in the EU28. Only a base case scenario for phthalate-attributable diabetes was calculated, no sensitivity analysis was provided.

For DDE, both a base-case and sensitivity analysis (high case) was provided in the Legler et al. study. In the base case scenario an odds ratio (OR, a rate for increased risks compared to unexposed groups) of 1,25 was used for DDE (Wu et al., 2013). This leads to 28.200 cases of diabetes in the EU that were attributable to DDE, which results in total costs of € 835 million. However, in the sensitivity analysis (high exposure scenario) of the Legler study, the DDE-attributed costs are even higher than the upper estimate in the HEAL study. For this latter estimate for DDE-related diabetes, an OR of 7,1 was applied (Turyk, Anderson, Knobeloch, Imm, & Persky, 2009), which results in 564.000 DDE-attributable cases at a cost of € 16,6 billion in total. This is a large difference between the ORs of both studies. The EDC-attributable factors are derived from two different ERRs; the base case attributable factor is derived from a near significant result from a meta-analysis on DDE (95% CI 0,94-1,66) (Wu et al., 2013), while the high scenario is based on one study by Turyk et al. (Turyk et al., 2009). Therefore, the sensitivity analysis (high exposure scenario) should most likely be interpreted as a worst-case scenario. Still, the amount of DDE-attributable cases (564.000) is similar to those

estimated in the HEAL study in its lower range, with 600.000 attributable cases (2% of 30 million diabetics).

If taking the base case scenarios from Legler and co-authors, the percentage of EDC-attributable cases is much lower than the 2% or 5% used in the study of HEAL. This difference is the driving factor between the distinct estimates for EDC-attributable cost of diabetes in both studies for the EU. It should be noted that the study of Legler only provides an estimate for two EDCs while HEALs calculation estimates the combined effect for all EDCs.

Summary

- The cost estimates per individual with diabetes are very different between HEAL (€ 10.000 per year), which includes both direct and indirect costs, and the study of Legler et al. (lifetime cost of € 29.600), including only direct cost;
- HEAL calculated a total annual cost range for the EU of € 6 – 15 billion for diabetes, while the range calculated by Legler et al. was wider with € 1,44 and 17,2 billion;
- In the base case scenario, Legler et al. calculated much lower attributable fractions leading to much lower amount of cases compared to HEAL, and therefore much lower costs in the lower estimate;
- The large difference between the lower and upper estimate in the study of Legler is related to a worst-case estimate amount of DDE-attributable cases (not related to phthalate). The amount of cases, however, is similar to the amount of EDC-attributable diabetes cases estimated by HEAL in its 2% estimate.

3.6.13. Increment death rate

A detailed overview of the breakdown of costs and study parameters is given in Annex B.

The cost for this health effect has been modelled in the Trasande studies by Hauser et al. (2015). The increment in death rate among men with a lower Testosterone (T) was based on the combination of two relationships: two phthalates lowered T in men aged 40-60 (Meeker & Ferguson, 2014) and decreased T leads to increased death rate among men aged 55-64 (Araujo et al., 2011). The phthalate study did not find such health effects for other age groups, other phthalates (13 metabolites were assessed in total), and for women. In addition, potential other effects of lower T levels on death rate, such as possibly a lower incidence of prostate cancer, were not considered. The combination of these two assumed relations, provide low strength to the link between phthalate and increased death rate in man, decreasing the certainty of the cost calculation for this health effect.

Indirect socio-economic cost

Only indirect non-healthcare cost to the increment of deaths was estimated by calculating lifetime economic productivity loss due to early death (Max, 2013). This paper was not published in peer-reviewed, public literature and was only cited in the supplemental material by the paper of Hauser et al.. Therefore, we were unable to specify or verify these costs any further. Hauser et al. describe that the cost was adjusted to an amount of € 320.700 per capita. The annual amount of deaths among men in the age group 55-64 in the EU is 241.000, of which 10,3% was calculated by Hauser et al. to be attributed to phthalate exposure based on the above mentioned assumptions. This leads to a total cost estimate of approximately € 8 billion.

4. Gaps and needs in "cost of EDC" estimates: a way forward using a modular approach

So far, the existing modelled socio-economic impacts of EDC-attributable costs are only based on a subset of the diseases that are linked to EDC exposure. Existing gaps in health-related cost estimates are identified in this chapter. Here, we propose a so-called "modular approach" that consists of "building blocks" of knowledge on certain EDC-related diseases and their socio-economic impacts. We apply this approach to a selected group of EDC-related health endpoints that have not been modelled before (endometriosis, neural tube defects and asthma), and two EDC-related health endpoints quantified earlier (ADHD an ASD). As such, data is provided on EDC-attributable socio-economic cost that have (not) been addressed in earlier studies, as well as information is deemed relevant for their interpretation. The modular approach provides a structured way to add new information on socio-economic cost of EDC-related health impacts in the future.

We argue that more structure, transparency, uniformity and completeness of information on socio-economic cost estimates is needed to enhance interpretation and comparability between estimated cost of different health effects. However, this methodology could also be applied in a broader perspective, to analyze any other health impact, potentially causal agent, and associated socio-economic costs.

4.1. Why a modular approach?

The existing modelled socio-economic burdens of EDC-associated health effects are based on a subset of the diseases that have been associated with EDC exposure (see Table 1). Hence, it could be argued that current EDC-related cost estimates represent "the tip of the iceberg" only. Additionally, the attributable fraction of EDCs to the onset of a disease might an over- or underestimation. Therefore, a flexible method is needed to implement progressing knowledge in these cost estimates and add novel cost estimates for EDC-associated health effects.

In the previous chapter, we have provided explanation on the (differences) in cost estimates for EDC-associated diseases and the uncertainties around these estimates. In this chapter, we introduce a modular approach to improve the transparency and understanding of socio-economic cost estimation of EDC-related health impacts. For that, we will:

- Identify gaps and needs on disease- and EDC-related information that is relevant for the modelling of socio-economic cost of various EDC-related health effects;
- Propose a standardized approach for presenting socio-economic costs, that allows inclusion of information that is relevant for the interpretation of data on socio-economic cost;
- Apply and provide this information for a selection of EDC-related health effects.

Considering the increasing knowledge of EDCs and their potential health impact, new diseases, disorders and conditions can be added to this overview, along with an estimate of their potential socio-economic costs. As such, this modular approach can gradually lead to a more complete understanding of the (potential) socio-economic costs of EDCs in Europe.

4.2. Methodology

The quantified health endpoints in other EDC-cost studies (Table 4) are compared to the total list of identified potential EDC-related health endpoints (Table 1) in order to identify main gaps in types of quantified endpoints. Next, an explorative literature search of cost-of-disease studies was performed to identify whether healthcare cost of these identified health effects have ever been quantified before, irrespective of the link with EDCs. For that, Scopus and Google were searched for the health effect + "socio-economic"/ "economic" + "cost" / "burden" / "impact". Then, an assessment was carried out to identify what information would be needed to enhance the understanding of the disease itself, the potential link between the disease, EDCs and ED-modulation, and an interpretation of socio-economic cost of health effects. This modular approach of information gathering was exemplified with three health effects that not have been modelled so far, *i.e.* endometriosis, asthma and neural tube defects, and two health effects that have been modelled before, *i.e.* AD(H)D and ASD. The relevant information was aggregated in a single fact sheet per health effect to provide a clear overview.

4.3. Data gaps in cost of health effects

As mentioned in Chapter 2 (Table 1), we have identified more than 80 different (potentially) EDC-related health endpoints, of which 13 health endpoints were quantified in previous studies of cost of EDC-related health effects (Chapter 3) (Bellanger et al., 2015; Hauser et al., 2015; HEAL, 2014; Legler et al., 2015; Olsson et al., 2014; Trasande et al., 2015). This leaves a large part of the potential EDC-related health effects from Table 1 unquantified. These mainly comprise of:

- Female reproductive effects: only female sub- and infertility was partially included in the calculation of HEAL;
- Immune-related disorders: no health effects quantified;
- "Other" EDC-related disorders (such as thyroid effects and neuroendocrine diseases): only one population effect on earlier death of males was quantified (Hauser et al., 2015).

The lack of quantified endpoints for immune-related disorders and the group of "other" EDC-associated effects could partially be attributed to the fact that the role of EDCs in immune diseases did not come into focus until recently and/or are more debated. Consequently, there are large data gaps regarding the effects of potential EDCs on immune disorders. However, for female reproductive effects there are many studies available assessing the relation to EDCs, also in humans, such as female reproduction effects in relation to DES exposure.

For most of the identified EDC-associated health effects, cost estimates were available. However, for 21 health endpoints no or limited studies were identified that quantified socio-economic costs of health effects. These endpoints are listed in Table 7. Due to the challenging character for providing a cost estimate for some endpoints, it is reasonable to assume that not all health effects will be quantified in the future. For instance, socio-economic costs of a shift in sex ratio (decline in male population) will be extremely difficult to quantify.

Table 7. Results of the 'quick scan' to identify gaps in data availability of cost-of-disease studies: health effects (potentially) related to EDCs, of which no or limited studies are available that quantify costs.

No (N) or limited (L) cost estimate available		Comment
Female Reproductive problems		
Reduced female fecundity (lower number of offspring	N	
Disturbed (decreased) lactation period	N	
Abnormal vaginal, cervical, uterine, and oviduct anatomy	N	
Reproductive tract abnormalities at the ovaries.	L	no cost estimate, but might be related to IVF and pregnancy outcomes
Premature thelarche	N	
Female idiopathic precocious puberty / early menarche	L	1 direct cost estimate (abstract only)
Female delayed puberty	L	
Disturbed menstruation cycle (Oligomenorrhea)	N	Not available, but potentially such costs have been modelled as a side effect of diabetes/obesity
Male reproductive problems		
Male reproductive organ abnormalities other than hypospadias and cryptorchidism (reduced testis weight, abnormal small penis, problems efferent ducts, altered AGD, morphology of seminiferous tubules, nipple retention)	N	
Testicular dysgenesis syndrome (TDS)	N	
Neurobehavioral disorders		
Psychomotor retardation, memory, learning problems	L	one paper cost learning problems from 1995
Hormone-related cancers (none)		
Metabolic syndromes		
Cardio protection	N	Is a *positive* effect, not a disease
Immune function, immune diseases and disorders		
Increase of systemic infectious diseases due to altered immune response (as a whole)	N	should be further specified what kind of infections
Increase of local infections due to altered immune response (as a whole)	N	should be further specified what kind of infections
Exanthema subitum	N	
Autoimmune thyroid disease (AITD) (e.g. Hashimoto's thyroiditis, idiopathic myxedema, asymptomatic thyroiditis, endocrine exophthalmus, and Graves' disease)"	N	
Other		
Sex ratio - declining male population	N	
Neuroendocrine disruption: Various diseases that affect the pituitary or hypothalamus	N	should be further specified
Adrenocortical hyperplasia (growth, stress response)	L	congenital variant; cost-effectiveness neonatal screening
Adult (sub)hypothyroidism	N	to be further specified by impacts
Thyroid resistance syndrome	N	

4.4. Identification of relevant information for the set-up of a modular approach for EDCs

An essential point within the modular approach is the presentation of socio-economic cost. Therefore, the health effects for which no or very limited data is available on socio-economic cost (Table 7) were not considered further in this report. For the other EDC-related health effects, general information on healthcare cost is available. Below we propose information deemed relevant for the interpretation of cost:

- A **general description** of the disease, such as development of the disease, key characteristics and diagnosis;
- Possible **treatment** of the disease (this could be, but is not necessarily related to what has been included as socio-economic cost, as literature sources used for both elements might differ);
- **Endocrine mechanisms or pathway(s)** involved in the diseases (as mentioned in prevailing reviews on EDCs and health effects, such as EU, UNEP/WHO);
- **Statements on the role of EDCs** and (potential) strength of the link with endocrine disruption (as mentioned in prevailing reviews on EDCs and health effects, such as EU, UNEP/WHO);
- **Potential EDCs** (or groups of EDCs) that have been associated to the health effect, their key references (from source epidemiological studies) and comments on observed relations. This information is relevant because it could provide a starting point for defining priorities for further studies and actions;
- **Comorbidities**. These are additional disorders or diseases (or their effect) potentially co-occurring with the primary disease or disorder. They provide an insight to possible relations between health effects. Comorbidities could be, but are not always, taken into account in the cost-of-disease estimates. Accounting for comorbidities will increase the risk for double-counting of costs. On the other hand, information on co-morbidities is very relevant to provide a complete estimate of potential socio-economic costs of health effect of specific compounds;
- Current **incidence** (newly diagnosed cases of a disease) **or prevalence** (number of cases of disease existing in a population). This provides information on the extent of the disease burden (population affected). Preferably, a recent, aggregate estimate of incidence or prevalence for the EU28 is available, as it varies between countries and among time. In addition, trends in incidence or prevalence could also be provided;
- **Socio-economic cost estimate**, which provides an indication on the impact of the disease on society. It is recommended that the cost information includes:
  - Key literature reference, for traceability of presented numbers;
  - Type of costs taken into account (direct, indirect and intangible cost) in order to interpret completeness of the cost data and compare results with other studies and health effects;
  - Cost estimate, as reported in the original study without adjustments;
  - Extrapolation to total annual cost in the EU28, so that the quality and extent of modification of the original study can be judged;
  - EDC-attributable fraction to be applied (see comments below);
  - Annual EDC-attributable cost for EU28. Finally, this present a best estimate (range) towards the potential socio-economic impact of EDCs.

All the presented information, such as cost data, incidence/prevalence, is based on a selection from available literature. Together, this information presents a summary and an overview of the current state of knowledge from prevailing literature, without pretending to be all-inclusive.

Presentation of modular approach: factsheet

We propose to visualize the information in a structured manner by means of a factsheet per health effect. In the factsheet, a concise summary of the relevant information (as identified above) can be provided. Over time and to meet specific needs, different types of information (categories) could be added, deleted or changed on the factsheets. Furthermore, the information on the factsheets need to be updated on a regular basis. This is especially the case for progressive scientific insights on EDCs, endocrine disruption and endocrine pathways/mechanisms. It is recommended to update the EDC-related information in concordance with updated publications on large, authoritative reviews, such as from the Endocrine Society, the EU (or EU bodies), and UN organizations such as the UNEP and the WHO. Regular update of information on disease incidence/prevalence, and socio-economic costs is also recommended.

Estimation of disease-specific socio-economic cost

The use of an EU-wide cost estimate is preferred. However, EU-wide studies are scarce and the quantification and extrapolation of non-EU or single country cost data towards the entire EU leads to high uncertainties. If a single-country estimate is available, an EU-wide can be generated by scaling to population size only. This approach was used previously by HEAL and the Nordic Council in their EU estimate of EDC-attributable cost. We used this approach also in this report for the selected diseases (neural tube defects, asthma and endometriosis). Extrapolation could be improved in the future by using more evidence-based correction factors such as medical inflation, GDP-PPP, EU prevalence/incidence rates and combining and weighting of different EU studies.

Range in EDC attributable fractions proposed for this modular approach

As discussed in section 3.4, one of the key challenges is to attribute a certain etiological fraction of the total disease cost, to a single cause, in our case exposure to EDCs in general or of specific chemicals. This is challenging because exact causes of disease development are usually not known, and often considered to be a complex interaction of e.g. genetic, dietary, environmental, occupational, behavioral aspects.

Previously, institutes have estimated the contribution of environmental factors to disease. In 2006, the WHO estimated that globally, nearly one quarter of all deaths and of the total disease burden can be attributed to environmental factors (WHO, 2006). This included modifiable parts (or impacts) of a wide range of environmental factors, such as pollution of air, water, or soil with chemical or biological agents, UV and ionizing radiation, noise, electromagnetic fields (EMF), occupational risks, the built environment, agricultural methods, climate- and ecosystem change, and hygiene (behavior). In contrast, a study on OECD countries concluded that 2.1 % - 5.0 % of the overall disease burden was attributable to the environment (Melse & De Hollander, 2001). The differences are, at least partially, explained by differences in methodology used and research scope, as well as differences in risk factors between industrialized and developing countries.

Only considering attributable fractions for chemical exposures, it was estimated in 2004 that globally 8.3% of deaths and 5.7% of DALYs were attributable to environmental exposure and management of selected chemicals (Prüss-Ustün, Vickers, Haefliger, & Bertollini, 2011). However, chemicals with

known health effects, such as dioxins, cadmium, mercury or chronic exposure to pesticides, were not included in that study due to data limitations. Another, earlier study on the environmental attribution of pollution, provided a similar estimate of 8–9% of the total disease burden (Briggs, 2003). Furthermore, disease-specific estimates towards the attribution of pollution were made, including diseases such as asthma, allergies, cancer, neuro-developmental disorders, congenital malformations, effects of ambient air pollution on birth weight, respiratory and cardiovascular diseases and mesothelioma (Mathews I., 2005), thereby providing a more disease-specific insight in the role of environmental pollution. However, it should be noted that most of the literature on EDCs and its role in the development of diseases has been generated in the past 10 years. The inclusion of these new insights could substantially improve the estimations of attributable fractions.

The estimates of environmental attributable fractions (EAF), or if available attributable fraction estimates for (chemical) pollution, can be used as a kind of upper limit to EDC-attributable fractions. For our modular approach, we chose **1%, 2,5% and 10%** as best estimate EDC-attributable fractions. The 1 and 2,5% point estimates are well within the (lower) EAF ranges presented in the previous mentioned papers of WHO and OECD, both for general environmental factors as for the contribution of pollution or chemicals specifically (Briggs, 2003; Melse & De Hollander, 2001; Prüss-Ustün et al., 2011; WHO, 2006). Beside the lower estimates, it must be recognized that for some diseases, environmental factors play a larger role in disease development and/or there is a stronger plausibility for hormone-related effects and evidence for the contribution of hormone disruption (e.g. certain hormone-related birth defects). Therefore, as an upper limit of the EDC-attributable fraction, we used a 10% EDC-attributable factor. This range accounts for uncertainties for the role of EDCs in disease development, yet recognizes that for some diseases the role of environmental factors is stronger than for other diseases. For the three diseases evaluated in this report, the best estimate EDC-attributable factors are well in line with reported EDC-attributable factors from the literature for these diseases (see also Table 8). It should be noted that, if more reliable information to underpin the EDC attributable fraction is available for specific health endpoints or of potential EDC substances related to health endpoints (as in the studies of Bellanger, Hauser, Legler and Trasande and co-authors) one can decide to use these estimates instead of or together with the values presented here.

Table 8. Breakdown of estimated EDC-attributable socio-economic cost for neural tube defects, endometriosis and asthma. Total potential annual EDC-attributable socio-economic costs for the EU28 are calculated using an EDC-attributable fraction.

Health endpoint	**Neural Tube Defects**	**Endometriosis**	**Asthma**
Reference	(Jentink, Van De Vrie-Hoekstra, De Jong-Van Den Berg, & Postma, 2008)	(Simoens et al., 2012)	(Suijkerbuijk et al., 2013)
Country of study	Netherlands	9 EU countries (DK+DE+NL+ BE+FR+IT+UK+HU+CH) + USA	Netherlands
Study population	Netherlands (in 2005 200.000 births per year of which 200 with NTDs)	society	541.943
currency / currency year	€ / 2005	€ / 2009	€ / 2007
Study perspective	Lifetime cost per child, disaggregated for different leasons	Societal cost and average cost per person	Societal cost (in the report also costs per person are provided)
Discounting	4%	0% (annual cost)	0% (annual cost)
Direct Healthcare Cost	Lifetime costs per child: Thoracal: € 107.263 Lumbal: € 108.178 Sacral: € 101.514	€ 15,9 billion (€ 3113 / person)	€ 287 million / society (€ 529 per person)
Direct Healthcare Cost approach	Total hospital care, paramedic care	Physician visits, medication, monitoring tests, surgery, other treatments, informal care, hospitalization	Physician visits, physiotherapy, hospital care, hospitalization, medication, nursing, influenza vaccination.
Direct Non Healthcare Cost	Lifetime costs per child: **Thoracal:** €19.272 **Lumbal:** € 21.317 **Sacral:** € 498	€ 0,9 billion (€ 168/person)	NA
Direct Non Healthcare Cost approach	Travel and parking cost for parents, wheelchair, house adaptions	Transportation, support household activities	NA
Indirect Healthcare Cost	NA	NA	NA
Indirect Non Healthcare Cost	Lifetime costs per child: Thoracal: € 151.663, Lumbal: € 146.377 Sacral: € 37.004	€ 32,4 billion (€ 6298 / person)	Absence (illness): € 258,9 million / society. Occupational disability: € 29,1 million - € 363 million /society
Indirect Non Healthcare Cost approach	Special education, productivity loss	Productivity loss	Productivity loss due to absence and occupational disability (low estimate: Friction method, high estimate Human Capital Approach)
Intangible cost	Age-specific quality of life, per year (cost not calculated) **Thoracal:** 0-10 years 0,3 / 11-21 years 0,18 / >21 years 0,3 **Lumbal:** 0-10 years 0,45 / 11-21 years 0,42 / >21 years 0,42 **Sacral:** 0-10 years 0,83 / 11-21 years 0,73 / > 21 years 0,79	An average of 0.809 QALY was reported in the first year after diagnosis (cost not calculated)	NA
Intangible Cost approach	Uses QALYs from earlier reports	QALY from questionnaire	NA
Total	€128.774 / case (weighted average cost per child, excluding QALY cost)	€ 49,2 billion / 9 EU countries combined (€ 9579 / person)	€ 575 million / society (occupational disability based on friction method)
Calculation / extrapolation (based on Eurostat 1 jan 2013)	25,755 million / year for NL. NL births= (176/5231) = 3,365% of total EU28 births in 2012.	9 EU countries population = 321,2 million = (321,2/505,7) = 63,5%	NL population = (16,8/505,7) 3,32% of total EU28.
EU28 total	€ 765,4 million	€ 77,5 billion	€ 17,3 billion
EDC-attributable fraction	1% / 2,5% / 10%	1% / 2,5% / 10%	1% / 2,5% / 10%
Reference and explanation of EDC-attributable fraction	An EAF for birth defects is estimated 5-10% (Smith, Corvalán, & Kjellstrom, 1999). 2,5% was used (Davies, 2006) correcting for other environmental causes and differences between developed and developing countries	EAF for maternal conditions (1-5%) in high income countries (Melse & De Hollander, 2001)	EAF of 10-35% (Landrigan, Schechter, Lipton, Fahs, & Schwartz, 2002). Coincides with estimate of 11% of chemical-attributable fraction (Prüss-Ustün et al., 2011)
Potential EDC-attributable cost	€ 7,65 / 19,1 / 76,5 million	€ 0,775 / 1,94 / 7,75 billion	€ 0,173 / 0,432 / 1,73 billion

4.5. Selection of health effects to test the modular approach

A qualitative approach was chosen to select health effects for further evaluation. The selection was based on expert judgement and team discussions on severity of the disease, incidence or prevalence, observations in the trends of incidence or prevalence, and availability of good-quality cost studies and other cost expertise. For none of the health effects, a detailed analysis for causation with EDC exposure was performed. A short rationale for the selected diseases is provided below.

- **Asthma.** Asthma is one of the most common immunological diseases for which cost estimates are readily available. It is generally recognized that, at least in genetically predisposed persons, environmental factors play a role in the development of asthma (Umetsu, McIntire, Akbari, Macaubas, & DeKruyff, 2002). Asthma is on the rise in developed countries. In the US, the prevalence of pediatric asthma has more than doubled over the past 20 years, and is now the leading cause of hospitalizations and school absenteeism (Landrigan & Goldman, 2011). As such, asthma is accounting for substantial healthcare and social cost.
- **Endometriosis.** Endometriosis is a common female reproductive tract disease (and important cause of female infertility) for which cost estimates are widely available in literature. The prevalence of endometriosis is high, affecting an estimated 6-15% of women in reproductive age (Kortenkamp et al., 2012), thereby potentially having a high societal impact.
- **Neural Tube defects.** Neural tube defects are rare birth defects but with severe implications for later life. Birth defects are the leading cause of infant death and are associated with substantial health and education costs (Landrigan & Goldman, 2011). Good quality cost studies are available that have quantified the socio-economic costs for neural tube defects.
- **Autism / Autism Spectrum Disorders (ASD).** A large number of children is affected by neurobehavioral disorders, including ASD and ADHD. ASD has been on the rise in the last decades (UNEP/WHO, 2013). Since it is not possible to cure ASD, the impacts on society are long-lasting and consequently very high.
- **Attention Deficit (Hyperactivity) Disorder (AD(H)D).** Similar to ASD, ADHD prevalence has been on the rise in the past decades (UNEP/WHO, 2013). It has now a high prevalence rate among children: about 4,5% in Europe (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007).

4.6. Application of the modular approach

For the socio-economic cost analysis, literature searches were performed to select the best applicable cost studies (recently published, relevant country, direct and indirect costs included). As an essential aspect of the modular approach, a breakdown of socio-economic cost for the three newly calculated EDC-associated effects is shown in Table 8. The various contributors to the cost are shown in a way that a distinction between various types of costs can be made. The information improves transparency and facilitates comparison between costs of different health effects. As clearly demonstrated in Table 8, EDC-attributable costs are strongly dependent on the total socio-economic cost. Therefore, it is of utmost importance to have a correct estimate of a disease-related health cost estimate. According to the presented calculations, the highest EDC-attributable socio-economic impact is expected for endometriosis. It should be noted, however, that there is a risk for double counting of socio-economic impacts of endometriosis. Female infertility is a secondary effect of endometriosis, and is partially included in cost estimate, as well as pelvic pain (Simoens et al.,

2012). It was shown that prevalence of endometriosis among infertile women was 47% (Meuleman et al., 2009). For an evaluation and breakdown of cost of ASD and AD(H)D, the reader is referred to chapter 3 and Annex B. A summary of the costs (for all five EDC-associated effects) is provided in the factsheets.

For the cost of asthma, the results of a recent Dutch study (Suijkerbuijk et al., 2013) were extrapolated to the EU28 population. The result, € 17,3 billion, seems to reflect a median cost estimate as opposed to other cost data available from literature that represent worst-case scenarios: € 3 billion for EU25 (van den Akker-van Marle, ME, Bruil, & Detmar, 2005) and € 72,2 billion for EU28 (European Lung Foundation, 2013). All studies include direct and indirect cost. In addition, the latter study includes indirect healthcare cost measured by DALYs. However, the inclusion of DALYs as well as the addition of three extra EU countries and use of more recent data can only partially explain the large difference between the studies.

4.7. Factsheets

A summary of all information considered relevant for the interpretation of the relation between the health effect, potential EDC-link, and socio-economic cost is provided hereafter in a summarizing factsheet per disease. These include three health effects that have not been quantified before, and two health effects of which EDC cost was previously quantified. Per disease, socio-economic cost is provided in the factsheet. For the three health effects addressed in this report (endometriosis, asthma and neural tube defects), a summary is presented on the breakdown of cost from table 8. For ADHD and ASD, a summary is presented on the cost estimated in studies of HEAL and Trasande and co-authors. An evaluation and breakdown of cost is given in chapter 3 and Annex B.

Neural tube defects (NTDs)

General description:

Neural tube defects are birth defects of the brain, spine, or spinal cord. They happen in the first month of pregnancy, often before a woman even knows that she is pregnant. The two most common neural tube defects are spina bifida and anencephaly. In spina bifida, the fetal spinal column doesn't close completely. There is usually nerve damage that causes at least some paralysis of the legs. In anencephaly, most of the brain and skull do not develop. Babies with anencephaly are usually either stillborn or die shortly after birth. Another type of defect, Chiari malformation, causes the brain tissue to extend into the spinal canal (U.S. National Library of Medicine, 2015)

Treatment:

Getting enough folic acid, before and during pregnancy prevents most neural tube defects. There is no cure for neural tube defects. The nerve damage and loss of function that are present at birth are usually permanent. However, a variety of treatments can sometimes prevent further damage and help with complications (U.S. National Library of Medicine, 2015)

Statements on the role of EDCs:

- The biological plausibility of a role for chemicals in developmental neurotoxicity [including neural tube defects] is strong (Kortenkamp et al., 2012)

Endocrine mechanisms / pathways:

According to (Kortenkamp et al., 2012):

- Thyroid disruption
- Sex hormone disruption
- Neuroendocrine disruption

Potential EDCs linked to health effect:

Chemical(s)	Key references epidemiology	Note
Pesticides: amide, benzimidazole, methyl carbamate, organophosphorus pesticides	(Rull, Ritz, & Shaw, 2006)	One study only
POPs: o,p'-DDT and metabolites, α-HCH, γ-HCH, and α-endosulfan	(Ren et al., 2011)	One study only
PCBs, dioxins, BFRs (incl PBDEs), perchlorate, pesticides, BPA, PFCs, phthalates, UV	(Boas, Feldt-Rasmussen, Skakkebæk, & Main, 2006; Boas, Main, & Feldt-Rasmussen, 2009; T. R. Zoeller, 2010)	Reviews on effect of environmental chemicals on thyroid function. Which chemicals are linked to NTDs are not specified

Comorbidities:

- Severe disability (Copp, 2008)
- Survival after birth (Copp, 2008)

Incidence / prevalence:

- 0.5-2 per 1000 births for severe NTDs (Copp, 2008)
- Mild NTDs include spina bifida occulta, incomplete formation of the neural arches of several vertebrae, which is usually asymptomatic and may be present in up to 10% of people (Copp, 2008)

Socio-economic cost estimate:

Total lifetime cost / individual	€128 774 discounted (4%) (Jentink et al. 2008)
Type of cost included	Direct and indirect healthcare and non-healthcare
EU28 cost / year	€ 765,4 million
EDC-attributable fraction	1% / 2,5% / 10%
EDC-attributable cost / year	€ 7,65 / 19,1 / 76,5 million

Endometriosis

General description:

Endometriosis is a common gynaecological disorder characterized by ectopic endometrium (presence of endometrial glands and stroma outside the uterus) causing benign endometrium-like inflammatory lesions outside the uterine cavity and is a major cause of chronic pelvic pain and infertility (Kortenkamp et al., 2012). Other symptoms include very heavy periods and pain in the lower back and abdomen. Some women have no symptoms at all (Kortenkamp et al., 2012; U.S. National Library of Medicine, 2015).

Treatment:

Diagnosis requires the identification of presence of endometrial glands and stroma outside the uterus on histologic inspection of biopsies obtained after laparoscopy. There is no non-invasive diagnostic tool available (adapted from (Kortenkamp et al., 2012). Treatment includes pain medicines and hormone therapy. Severe cases may need surgery. There are also treatments to improve fertility in women with endometriosis (Kortenkamp et al., 2012; U.S. National Library of Medicine, 2015).

Statements on the role of EDCs:

- Recent developments implicate developmental exposures to exogenous chemicals in heritable epigenetic changes that may contribute the disease development (Kortenkamp et al., 2012).
- Exposure to oestrogen or to oestrogenic EDCs is an accepted risk factor for breast cancer, endometriosis, fibroids and polycystic ovarian syndrome (PCOS) in women (European Environment Agency, 2012)
- The evidence is accumulating of correlations between EDCs in the circulation of women with endometriosis, although a cause-and-effect relationship has yet to be established, which is not uncommon in reproductive environmental toxicity (Diamanti-Kandarakis et al., 2009)
- There are sufficient data linking exposure to EDCs (phthalates, PCBs and dioxins) with endometriosis. Still it is classified as "limited and conflicting experimental and epidemiologic evidence" (UNEP/WHO, 2013).

Endocrine mechanisms / pathways:

- Estrogen dependent (role in apoptosis, invasion and adhesion, angiogenesis, proliferation).
- Progresterone (role in invasion and adhesion of endometrial tissue), role of estradiol and progresterone in angiogenesis of endometriotic lesions (Kortenkamp et al., 2012)

Potential EDCs linked to health effect:

Chemical(s)	Key references Epidemiology	Note
Phthalates	Buck Louis et al., 2013; Calafat et al., 2010	Various studies with and without association: - at least 6 studies with positive association - at least 2 studies with small/indicative association - at least 4 studies without association/no conclusion possible
Dioxins	Tsukino et al., 2005	Various studies with and without association
OCP: β-HCH, γ-HCH, Mirex	Upson et al., 2013, Buck Louis et al., 2012	Various studies with and without association
PCBs	Buck Louis et al., 2012; Porpora et al., 2009	Various studies with and without association
DES	Matalliotakis et al., 2008	

Comorbidities:

- PCOS, uterine fibroids and endometriosis are leading causes of sub fecundity and infertility (UNEP/WHO, 2013). 47% of infertile women had endometriosis (Meuleman et al., 2009)
- Increased risk of endometrial and clear cell ovarian cancer, non-Hodgkin's lymphoma, and atopic disorders (Giudice, 2010)
- The pelvic pain associated with endometriosis is a major cause of disability and compromised quality of life. Early menarche, short and heavy menstrual cycles, and cycle irregularity are risk factors for endometriosis (UNEP/WHO, 2013)
- Prevalence of immune disorders such as rheumatoid arthritis, systemic lupus erythematosus, hypo- or hyperthyroidism, and multiple sclerosis was higher in women with endometriosis than the general population (McLeod & Retzloff, 2010; Viganò, Parazzini, Somigliana, & Vercellini, 2004)

Incidence / prevalence:

- Occurs in 10-15% of women of reproductive age (15-49) and a minimum of 176 million women worldwide (UNEP/WHO, 2013)
- It occurs in 6–10% of women (Diamanti-Kandarakis et al., 2009)
- Estimates of the prevalence of endometriosis vary widely between 6-15% of women of reproductive age (Kortenkamp et al., 2012; Meuleman et al., 2009).

Socio-economic cost estimate:

Annual average cost / women	€ 9.579 (Simoens et al., 2012) (weighted average 9 EU countries)
Type of cost included	Direct healthcare and indirect non-healthcare
EU9 total cost / year	€ 49,2 billion
EU28 cost / year	€ 77,5 billion
EDC-attributable fraction	1% / 2,5% / 10%
EDC-attributable cost	€ 0,775 / 1,94 / 7,75 billion

Asthma

General description:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

The development of asthma appears to involve the interplay between host factors (particularly genetics) and environmental exposures that occur at a crucial time in the development of the immune system. A definitive cause of the inflammatory process leading to asthma has not yet been established. Considering innate immunity, numerous factors may affect the balance between Th1-type and Th2- type cytokine responses in early life and increase the likelihood that the immune response will downregulate the Th1 immune response that fights infection and instead will be dominated by Th2 cells, leading to the expression of allergic diseases and asthma. This is known as the "hygiene hypothesis". (NIH: National Heart, Lung, and Blood Institute, 2007)

Treatment:

Medications for asthma are categorized into two general classes: long-term control medication used daily to achieve and maintain control of persistent asthma, and quick-relief medication to treat acute symptoms and exacerbations. (NIH: National Heart, Lung, and Blood Institute, 2014)

Statements on the role of EDCs:

- There are also some indications that exposure *in utero* and during early life may increase the likelihood and severity of asthma development (Kortenkamp et al., 2012).
- There are good epidemiological data associating exposure to phthalates with asthma and other airway disorders. Endocrine mechanisms are not, however, clear. (UNEP/WHO, 2013)

Endocrine mechanisms / pathways:

- Developmental immunotoxicity (DIT) caused by EDC exposure may be one early-life immune insult. Exact endocrine mechanisms are, however, not clear (UNEP/WHO, 2013).
- The three major endocrine axes influence the immune system (hypothalamic–pituitary–adrenal (HPA), hypothalamic–pituitary–thyroid (HPT) and hypothalamic–pituitary–gonadal (HPG) axes), as well as several other neuroendocrine factors (Kortenkamp et al., 2012)

Potential EDCs linked to health effect:

Chemical(s)	Key references Epidemiology	Note
Phthalates	(Bornehag et al., 2004; Jaakkola et al., 1999; Oie, Hersoug, & Madsen, 1997)	Various studies found a relation with residential presence to PVC, as well two studies describe a correlation with DEHP in indoor dust and asthma
Triclosan, parabens	(Bertelsen et al., 2013; Savage, Johns, Hauser, & Litonjua, 2014; Spanier, Fausnight, Camacho, & Braun, 2014)	Suggested via evidence for allergic sensitization and coincidence with asthma exacerbations
PCBs, dioxins	(Stølevik et al., 2011; Weisglas-Kuperus, Vreugdenhil, & Mulder, 2004)Stolevik 2013 (PCBs, dioxins), Weisglas-Kuperus 2004 (PCBs	Suggested via increase of wheeze and infections
BPA	(Midoro-Horiuti, Tiwari, Watson, & Goldblum, 2010)	Toxicological and in vivo evidence only

Comorbidities:

- Respiratory conditions for which a pathophysiologic link to asthma is believed to exist are allergic rhinitis, sinusitis and otitis media. >25% of children have one or more of these comorbidities vs <10% of non-asthmatic children (Grupp-Phelan, Lozano, & Fishman, 2001)

Incidence / prevalence:

- It is one of the most common long-term diseases of children. In the US in 2009, 1 in 11 children had asthma and 1 in 12 adults (CDC, 2014)
- A total EU prevalence of 7,2% is reported (van den Akker-van Marle, ME et al., 2005)

Socio-economic cost estimate:

Annual total cost / person	€ 1.058 (Suijkerbuijk et al., 2013)
Type of cost included	Direct healthcare and indirect non-healthcare (based upon friction method)
Annual total cost / Netherlands	€ 575 million
EU28 cost / year	€ 17,3 billion
EDC-attributable fraction	1% / 2,5% / 10%
EDC-attributable cost	€ 0,173 / 0,432 / 1,73 billion

Autism & Autism Spectrum Disorder (ASD)

General description:

Autism spectrum disorder (ASD) is a neurological and developmental disorder that begins early in childhood and lasts throughout a person's life. It affects how a person acts and interacts with others, communicates, and learns. It includes what used to be known as Asperger syndrome and pervasive developmental disorders (U.S. National Library of Medicine, 2015).

Treatment:

There is no one standard treatment for ASD. Treatments include behavior and communication therapies, skills training, and medicines to control symptoms (U.S. National Library of Medicine, 2015). Individuals with ASDs can differ greatly in their clinical and functional presentation, resulting in potentially substantial differences in costs of treatment, care, and support. Typical cost includes special education, residential care and/or supported accommodation, and employment support (Buescher et al., 2014).

Statements on the role of EDCs:

- The biological plausibility of a role for chemicals in developmental neurotoxicity [including ASD] is strong (Kortenkamp et al., 2012). However, the complexities of studying human conditions and the issues of species extrapolation mean that strong evidence to link complex human disorders, like autism, to single chemicals or mixtures of chemicals has not emerged
- Sufficient evidence that environmental factors contribute to the increases in ASD. Sufficient evidence that exposure to some industrial chemicals is plausibly related to the production of neurobehavioral disorders (UNEP/WHO, 2013).
- Low strength of human evidence; moderate strength of toxicological evidence (Bellanger et al., 2015; Trasande et al., 2015)

Endocrine mechanisms / pathways:

- Thyroid disruption
- Sex hormone disruption
- Neuroendocrine disruption

(Kortenkamp et al., 2012; UNEP/WHO, 2013; WHO, 2014)

Potential EDCs linked to health effect:*

Chemical(s)	Reference	Note
Low molecular weight (LMW) phthalates	(Miodovnik et al., 2011)	This study also included other chemicals, and showed no effect of BPA on ASD
Pesticides	(Roberts et al., 2007)	Specific EDC-component not specified

* Perinatal exposure, reviewed (De Cock, Maas, & Van De Bor, 2012)

Comorbidities:

- 40% to 60% of people with ASDs also have intellectual disability (ID) (Buescher et al., 2014)
- Other comorbidities include ADHD, epilepsy, gastrointestinal symptoms, sleep problems, feeding problems and toileting problems (reviewed in (Mannion & Leader, 2013))

Incidence / prevalence:

- Autism spectrum disorders now occur at a rate that approaches 1% (UNEP/WHO, 2013)
- 'Classical autism' in the EU could be estimated as varying from 3.3 to 16.0 per 10 000. But these rates could increase to a range estimated between 30 and 63 per 10 000 when all forms of ASD are included (EC, 2005)

Socio-economic cost estimate:

Reference	HEAL (HEAL, 2014)	Trasande and co-authors (Bellanger et al., 2015)
Cost estimate	UK: aggregate costs for adults amount to £25 billion each year (Knapp et al., 2009)	€ 630.000 discounted (3,5%) lifetime cost per individual (adapted from (Buescher et al., 2014))
Type of cost included	Direct healthcare and indirect non-healthcare	Direct healthcare and indirect non-healthcare
EU28 cost / year	€ 226 billion	Not calculated
EDC-attributable fraction	2% - 5%	0,97% (low), 2,425% (base case), 4,85% (high) = respectively 126, 316 and 631 cases/year in the EU
EDC-attributable cost	€ 4,52 – 11,3 billion	€ 80 million (low) € 199 million (base case) € 399 million (high)

Attention Deficit (Hyperactivity) Disorder (AD(H)D)

General description:
ADHD and ADD are characterized by problems with attention, impulsivity and (in case of ADHD) hyperactivity. Childhood ADHD is likely to persist into adulthood and may constitute a lifelong impairment. The diagnostic criteria for disorders such as ADHD are variable, and changes in diagnostic practice are the probable reason for any apparent increase in incidence over time (Kortenkamp et al., 2012)

Treatment:
Treatment may include medicine to control symptoms, therapy, or both. (U.S. National Library of Medicine, 2015).

Statements on the role of EDCs:
- The biological plausibility of a role for chemicals in developmental neurotoxicity [including ADHD] is strong (Kortenkamp et al., 2012).
- Low-to-moderate strength of human evidence; strong strength of toxicological evidence (Bellanger et al., 2015; Trasande et al., 2015)
- Sufficient evidence that exposure to some industrial chemicals is plausibly related to the production of neurobehavioral disorders. (UNEP/WHO, 2013).

Endocrine mechanisms / pathways:
- Thyroid disruption
- Sex hormone disruption
- Neuroendocrine disruption

(Kortenkamp et al., 2012; UNEP/WHO, 2013; WHO, 2014)

Potential EDCs linked to health effect:*

Chemical(s)	Key references Epidemiology	Note
Polychlorinated biphenyls (PCBs)	(Sagiv et al., 2010)	∑PCB 118, 138, 153, 180
OPs (dialkyl phosphate (DAP) in urine)	(Marks et al., 2010)	
chlorpyrifos	(Rauh et al., 2006)	
BPA	(Braun et al., 2009)	Non-significant result
Polybrominated diphenylethers (PBDEs)	(Chen et al., 2014; Eskenazi et al., 2013)	
Low molecular weight (LMW) phthalates	(Engel et al., 2010)	Non-significant result

* Perinatal exposure, reviewed (De Cock et al., 2012)

Comorbidities:
- In children: oppositional defiant disorder and developmental coordination disorder (Kadesjö & Gillberg, 2001)
- In adults: alcohol and drug abuse, antisocial personality disorder and depression (Torgersen, Gjervan, & Rasmussen, 2006)

Incidence / prevalence:
- ADHD and ADD have a worldwide pooled prevalence estimate of about 5,3%; pooled prevalence in Europe is 4,5% (Polanczyk et al., 2007)

Socio-economic cost estimate:

Reference	HEAL (HEAL, 2014)	Trasande and co-authors (Bellanger et al., 2015)
Cost estimate	UK: £ 78 million / year (€ 56 per person) (Schlander, 2007)	€ 9860 - € 14483 / person per year (Le et al., 2014) adapted to € 77.000 discounted (3%) lifetime cost per individual
Type of cost included	Medication only	Direct healthcare and indirect non-healthcare for individuals with AD(H)D and their family members
EU28 cost / year	€ 0,72 billion	Not calculated
EDC-attributable fraction	2% - 5%	For OPs: 10,76% (low), 17,28% (base case), For PBDE: 12,53% (base case) Together 42.000 – 54.0000 cases/year in the EU
EDC-attributable cost	€ 14 – 35 million	For OPs and PBDE combined: € 2,62 billion (low) € 4,14 billion (base case) € 4,93 billion (high)

5. Evaluation

In this chapter, an overall evaluation of the available data on EDC-associated health endpoints and possible EDC-related cost is made. In addition, newly modelled costs estimates are provided in this report. This results in a range for potential annual EDC-related socio-economic cost for the EU28. With an improved understanding of the socio-economic costs associated with EDCs, we discuss which areas might have highest estimated health impact and priorities that may be addressed in risk governance and research.

5.1. Range for EDC-attributable cost in EU28

In Table 9, a range is presented for EDC-attributable socio-economic cost per health effect and a total for the EU28 that were calculated in this report and previously by others. The socio-economic cost estimates include estimates for the three health effects that were added in the modular approach in this report as well as an additional estimate for IQ loss (Rijk & van den Berg, 2015). The lowest and highest estimates available from the various studies reflected in this report have been used to determine a cost range for each health effect. Taking into account the overlap and differences between the quantified health effects, *the range of total socio-economic cost for EDC-attributable health effects is estimated to be between € 61 billion and € 293 billion annually for the EU28.*

In the evaluation of the composition of cost in Chapter 3.6, we have identified some discrepancies in cost estimates that affect the overall cost estimates. Below, we argue to adjust some of these low – and/or high base estimates in order to align cost estimate assumptions across diseases and justify the addition of EDC-attributable health costs in our modular approach. Consequently, this will ideally lead to a more realistic estimate of healthcare cost that are associated with EDC exposure in EU28.

Proposals for adjustments of the cost range

In Table 9 we propose adjustments to certain EDC-attributable cost. The first cost estimate that is likely overestimated is the cost for male fertility. The highest range estimate is based on the number of couples of reproductive age and the assumption that they all want to become pregnant if not using (documented) contraception. The other estimates are based on the number of registered infertile couples from healthcare registries or the amount of ART treatment cycles. The latter estimates seem to better represent the number of infertile cases. Therefore, we believe it is reasonable to take the second highest estimate as upper limit for EDC-attributable cost of male infertility.

The highest contributors to the total cost are the neurodevelopmental and -behavioral diseases and disorders. Here, especially the contribution of IQ loss (or foregone IQ points) is driving the cost estimate. It was shown that almost every newborn child could lose some IQ points due to (mostly) prenatal exposure to EDCs. It should be noted, however, that socio-economic impact of IQ loss is calculated based on indirect loss, i.e. income loss due to lower IQ and hence does not represent actual expenditures (such as medications and treatments). In both cost estimates, the costs for IQ loss were estimated according to the best applicable knowledge and accepted methodology for valuation of IQ points from the US EPA (US EPA, 1997) for environmental impacts. Somewhat lower results were derived from a study in the Netherlands (Rijk & van den Berg, 2015), replacing the lower estimate from Trasande et al. (2015). Possibly, the EDC-attributable cost for IQ loss is overestimated

due to differences in income structure between the EU and the US. Also, a potential interaction with the increasing trend in IQ over the past decades is not taken into account. However, there is insufficient data available to propose a further adjustment of the presented socio-economic impact due to loss of IQ.

Apart from IQ loss, the cost for other neurodevelopmental and -behavioral health effects are also relatively high compared to other groups of health effects that have been linked to EDCs. These cost largely comprise of direct healthcare cost, provided by specialized institutes and residential care. The lowest estimate for AD(H)D, however, is most certainly an underestimation because it only takes into account cost of medication, while the amount of expected other direct and indirect treatment costs related to AD(H)D is substantial, as argued in the paper of Bellanger et al. (2015). Therefore, it is proposed to replace this low estimate with a higher estimate that is based on a more representative set of costs.

The increment in death rate due to a lower level of Testosterone (T), is based on two assumed links, making the cost estimate more uncertain. The EDC-attributable factor for this health endpoint was calculated 10,3%. As described in paragraph 4.4, we used 1% (low), 2,5% (base) and 10% (high) as estimate EDC-attributable fraction in our modular approach. Applying a similar approach, the 10,3% would categorize as high case estimate for increment death rate due to EDC exposure. We propose to add a 1% AF as low case estimate, which amounts to € 0.8 billion.

When taking the adjusted EDC-attributable cost estimates into account, the range of EDC-related costs amounts to € 46 – 288 billion for EU28, annually. Especially the contribution of IQ loss (€ 32-184 billion) dominates the cost estimate. With the modular approach applied in this report, the EDC-related health effects endometriosis, neural tube effects and asthma possibly add € 2,4 billion (€ 1-10 billion) to the total cost estimate range. However, considering the uncertainties in cost calculations and potential EDC-attributable fraction, these estimates should be considered with care.

5.2. Availability and (un)certainty of data

Gaps in quantified health effects

In Table 10, an overview of health effects is presented for which EDC-associated costs were quantified in this and other reports, and health effects of which no or limited cost data was available in the public literature. It is clear that especially the costs of female reproductive health effects, immunological effects and "other" effects (e.g. neuroendocrine diseases, thyroid effects, bone disorders) are underrepresented in the recent cost estimate papers. There might be several reasons why these have not been quantified. A reason might be that the link with EDCs is not well specified (yet) or has only recently become focus of scientific studies. This is for example the case with immune-related disorders. In addition, for some health effects it might difficult to quantify socio-economic costs, because there is no published literature available on healthcare costs or cost calculations are in a preliminary stage, e.g. for altered onset of puberty and menopause or for altered sex ratio.

Table 9. Range of EDC-attributable cost per health effect and total EDC-attributable socio-economic cost estimates for EU28 (in billion €). Outliers in cost estimates and their proposed adjustments are indicated in red.

Source	Nordic Council			HEAL		Trasande *et al.*			This report			overall range		Adjusted range	
etiological fraction / type of estimate	**2%**	**20%**	**40%**	**Total (2%)**	**Total (5%)**	low	base case	high	**1%**	**2,5%**	**10%**	**lowest**	**highest**	lowest	**highest**
Reproductive tract and fertility															
Reduced female fertility				0,048-0,062	0,120-0,155										
Reduced male fertility	0,007	0,072	0,145			4,71	4,71	4,71				**0,007**	**4,71**	**0,007**	**0,155**
Cryptorchidism	0,018	0,181	0,363	0,018-0,026	0,045-0,065	0,117	0,130	0,130				**0,018**	**0,363**	**0,018**	**0,363**
Hypospadias	0,009	0,089	0,178									**0,009**	**0,178**	**0,009**	**0,178**
Endometriosis									0,775	1,94	7,75	**0,775**	**7,75**	**0,775**	**7,75**
Neurobehavioral diseases and disorders															
Autism spectrum disorders (ASD)				4,52	11,3	0,080	0,199	0,399				**0,080**	**11,3**	**0,080**	**11,3**
AD(H)D				0,014	0,035	2,62	4,14	4,93				**0,014**	**4,93**	**2,62**	**4,93**
IQ loss						42,2	133,4	183,6	32,0	84,3	136	**42,2**	**183,6**	**32**	**183,6**
Mental retardation						6,11	22,6	33,43				**6,11**	**33,4**	**6,11**	**33,4**
Neural tube defects									0,008	0,019	0,077	**0,008**	**0,077**	**0,008**	**0,077**
Hormone-related cancers															
Breast cancer				0,320	0,800							**0,320**	**0,800**	**0,320**	**0,800**
Prostate cancer				0,180	0,450							**0,180**	**0,450**	**0,180**	**0,450**
Testis (testicular germ cell) cancer	0,025	0,249	0,499			0,313	0,848	0,848				**0,025**	**0,848**	**0,025**	**0,848**
Metabolic syndromes, immune disorders, other															
Obesity child				1,62	4,05	1,56	1,56	1,63				**1,62**	**17,2**	**1,62**	**17,2**
Obesity adult						15,6	15,6	15,6							
Diabetes mellitus (type 2)				6,0	15,0	1,44	1,44	17,2				**1,44**	**17,2**	**1,44**	**17,2**
Increment death rate among men						7,96	7,96	7,96	0,80			**7,96**	**7,96**	**0,80**	**7,96**
Asthma									0,173	0,432	1,73	**0,173**	**1,73**	**0,173**	**1,73**
TOTAL (billion €)	**0,059**	**0,591**	**1,185**	**12,7**	**31,6**	**44,7**	**192,6**	**270,4**	**NA**	**NA**	**NA**	**60,9**	**292,6**	**46,2**	**288,0**
TOTAL (billion €) after correction			**NA**		**NA**		**157 (90% C.I. 32 – 212)**				**NA**		**NA**		**NA**

Note: Cells have been merged if they reflect cost estimates of combined health effects. For the studies of Trasande et al. the low and/or high estimates are provided as kind of sensitivity analysis; if these low and/or high estimates were not given, the base case estimate has been noted (in grey) to calculate an upper and lower boundary of total EDC-related healthcare cost.

Type of cost data included in socio-economic cost estimates and methodology to calculate costs

In general, the types of costs taken into account and the methods used to calculate costs largely influence socio-economic cost estimates. For instance, a cost estimate including direct, indirect and intangible costs is likely to be significantly different from a cost estimate only including direct costs, as has been illustrated by various examples within this report. For example, the direct cost for female adult obesity is estimated about € 20.000, while intangible costs were valued at almost € 270.000, thus adding a significant amount.

For health endpoints for which cost studies are available, all cost studies have addressed direct cost of healthcare (except for IQ loss), such as medication and hospital treatment. For most endpoints, also indirect non-healthcare effects are quantified, which are mainly productivity losses due to morbidity and mortality of patients and their caregivers. Less often, direct non-healthcare effects are quantified, such as travel cost and childcare cost when treatment is received. However, the majority of these costs are negligible compared to medical cost and productivity losses. Other types of costs that are not often included in socio-economic cost evaluations are indirect healthcare cost and intangible cost. Indirect healthcare costs are most often expressed in DALYs. Intangible costs are most often expressed in QALYs, and are valued using a standard cost per QALY lost. QALYs represent the opposite of DALYs (a gain in years living in good quality of health, versus a loss of years due to living in disability or early mortality). DALYs and QALYs can therefore not be added up. DALYs and QALYs, when quantified, usually result in high total costs because both are often valued at approximately € 70.000 per year.

Since there is a difference in interpretation in types of costs, it would be interesting to separate costs related to direct cost ("real" expenditures) from indirect costs and intangible costs (cost that place a burden on society or on the quality of lives, that usually do not represent real expenditures). As a result, it would be easier to interpret individual disease-related cost estimates and compare them with other similar cost estimates (e.g. national of European health care budgets).

Furthermore, the methodology used to calculate costs influence the results as well. Cost-of-disease studies using a bottom-up approach (calculating cost per individual and extrapolating this to the whole population) tend to overestimate the burden of societal costs (as seen in top-down cost studies, where actual healthcare expenditures are analyzed and broken down to cost per patient). Furthermore, if lifelong health impacts are calculated (e.g. for ASD), or effects that will occur in the future (e.g. for cancer risk) it makes a large difference whether costs have been discounted and what rate for discounting is used. For instance, if costs will occur 30 years after exposure, discounting at a rate of 4% may lower annual cost with approximately 50%. With regard to indirect costs, there are two main methods to estimate productivity loss: the friction method and the human capital approach. In most cases, the human capital approach (neglecting replacement of ill workers by new workers) leads to much higher cost for productivity losses. Other parameters, including currency, year of study and geographic differences, apparently have a minor influence on estimated cost, when applied to relatively similar scenarios of cost estimation.

European-wide data is favorable but often not available

The use of data on incidence or prevalence of a disease usually does not contribute to a high uncertainty in cost estimates. In general, these data are available from reliable disease registers.

However, differences in healthcare organization (e.g. how a diagnosis is made, methods of treatment applied), environment, income and lifestyle can influence prevalence and incidence rates and the health care expenditures per case and consequently the related total healthcare costs. This could lead to problems when extrapolating from one subpopulation or country to another. To eliminate a potential extrapolation error, it is therefore preferred to use not only European estimates for prevalence or incidence for a certain health effects, but also a European-wide cost estimates. However, to our knowledge, recent European-wide cost estimates for cost of EDC-related diseases are limited, with the exception of relatively recent cost data for cancer (Luengo-Fernandez et al., 2013), various brain disorders (Gustavsson et al., 2011; Olesen et al., 2012), cardiovascular disease (Leal, Luengo-Fernandez, & Gray, 2012), obesity (Müller-Riemenschneider, Reinhold, Berghöfer, & Willich, 2008), and osteoporosis (Hernlund et al., 2013). For some EDC-related diseases, cost estimates have been published and aggregated for multiple countries, e.g. diabetes (5 EU countries) (Kanavos et al., 2012) and endometriosis (9 EU countries) (Simoens et al., 2012). The use of recent European-wide estimates would clearly improve reliability of the cost estimates of EDC-related health effects.

No standardized approach for socio-economic cost evaluation

Although the type of costs taken into account strongly influences the resulting cost estimate, there is no standardized approach for socio-economic cost evaluations of health effects. This clearly hampers interpretation and comparison of costs for different diseases.

When considered in a cost-effectiveness evaluation (cost-benefit analysis), such cost estimates may provide input for certain policy decisions. Therefore an inclusion or exclusion of certain cost aspects may have a high impact. In such cases, the scope of study is of high importance. A general recommendation is to develop a standardized cost estimate approach for cost-benefit evaluations in the context of hazardous substances. It would be desirable to set criteria what kind of cost should be included and what methodology should be used in order to assure the validity of the cost estimate. At least, for transparency, background parameters for the cost of disease study should be provided, as is proposed in the modular approach presented in this report. As such, differences can be explained by looking to crucial parameters and type of costs taken into account.

Use of an EDC-attributable fraction versus exposure-response relations

One of the major challenges is to use a reliable EDC-attributable fraction to estimate the fraction of total cost that could be related to EDC exposure. To establish an attributable or etiological fraction for a single cause to a disease, is not only a challenge for EDCs and their attribution to health effects, but is a general scientific challenge for all factors influencing development of diseases. Diseases usually have a multifactorial origin, and the exact onset of disease remains unexplained in most of the cases. An estimation of socio-economic cost based on a single factor, whether this is exposure to EDCs or another cause, remains a simplification of reality. For quantification of the socio-economic costs, the EDC-attributable fraction remains a very influential parameter that highly influences the final outcome of a socio-economic cost evaluation. A substantial over- or underestimation of EDC-attributable cost due to a wrong estimate of the attributable fraction is therefore realistic.

As explained in Chapter 3.6 and 4.4, EDC-attributable fractions can be calculated from selected exposure-response relations (ERRs) in epidemiological studies. This approach was followed in the studies of Trasande and co-authors. Unfortunately, not for all of the health effects and suspected

compounds is epidemiological evidence available. The estimates are highly dependent on availability of exposure and (human) effect studies, general quality, representativeness to the desired population, and selection (bias) to determine an ERR. Not unimportantly, with the available research budgets and time needed to establish ERRs in high quality studies, it is highly unlikely that biomonitoring data and epidemiological results will become available for *all* chemicals (and mixtures) on the market and *all* types of EDC-associated diseases.

Furthermore, there is currently no (legislative) framework that requires studies on the mode of action of a chemical when it is brought to the market. At present, the required toxicological data within regulatory frameworks is not sufficient to establish an attributable fraction of a chemical to a disease. The alternative, i.e. to wait for epidemiological data to become available, is clearly impossible and unethical. Therefore, assumptions will have to be made to establish an etiological fraction for the contribution of EDCs to disease. Using a best estimate of a predefined etiological fraction could be criticized as being a "wild guess" but is a transparent approach, easy to interpret and modify if needed (e.g. as new insights on EDCs arise providing arguments for adjustments upwards or downwards), aggregates the effects of EDC mixtures, and is widely applicable to all diseases in absent of better information.

Interestingly, most ERR-derived EDC-attributable fractions that were evaluated in this report were well in line with EDC-attributable best estimates applied in other studies as well as acknowledged estimates for environmental contributions to disease burden. Therefore, we believe that even when there is limited information available, it is valid to use (a range of) best estimates as starting point to determine the EDC-attributable fraction of a health effect.

5.3. Highest cost and possible implications for priority setting

In this report, we have shown that even at low-range estimates, the socio-economic impact on society might be substantial and that the financial burden for the EU and its future generations is potentially high. In view of the potentially high socio-economic costs associated with EDCs, further action might be warranted. It could be stressed that uncertainties and discussions about (potential) health effects should not hamper or delay further actions or interventions on EDCs.

Actions based on measured effects and (in case of data limitations) on precautionary principles, might be warranted, yet are currently hampered by a variety of reasons as also depicted in this report. The phenomenon of uncertainty hampering public health policy action on toxic chemicals and their health effects was well described by Michaels in the context of hazardous chemicals (Michaels, 2006): "*Absolute certainty in the realm of medicine and public health is rare. Scientists must extrapolate from study-specific evidence to make causal inferences and recommend protective measures. Absolute certainty is rarely an option. Our regulatory programs will not be effective if such proof is required before we act; the best available evidence must be sufficient*".

Also, if applying the International Risk Governance Council (IRGC) risk management framework (introduced in Chapter 1) it can be said that for EDCs, the 'precautionary approach' of risk management could be appropriate. The IRGC defines generic risk management strategies to classes of risks based on the distinction between complexity, uncertainty, and ambiguity. According to the IRGC, a complex risk is often associated with major scientific dissent about complex dose-effect relationships. According to the IRGC, the management of risks characterized by multiple and high uncertainties should be guided by the *precautionary approach*. Since high uncertainty implies that

the (true) dimensions of the risks are not (yet) known, one should pursue a cautious strategy that allows learning by restricted errors (IRGC, 2012). Besides uncertain and complex, the issue of EDCs can also be categorized as an ambiguous risk according to the IRGC as divergent or contested perspectives on the justification exist, severity or wider meanings associated with a given threat. According to the IRGC this requires a *''discourse-based' strategy, which seeks to create tolerance and mutual understanding of conflicting views and values with a view to eventually reconciling them.'*

Although not all EDC-associated health effects have been or can be quantified, this report might help prioritization of further areas for research and actions on EDCs.

When considering measures, more research to identify EDC-related effects, strength of evidence, endocrine mechanisms, mode of actions, and attributable fractions to a certain effect could be very relevant to reduce uncertainty and improve understanding. Standard tests that are requested for chemicals on the market do not cover many apical endpoints that have been associated with EDCs, such as immunotoxic effects, neurotoxic effects and diseases of the thyroid. As a result, this type of information will not become available within the legislative frameworks and existing data gaps will remain unsolved.

The highest cost of EDC-associated health effects, are found in the group of neurobehavioral diseases, disorders and cognitive conditions. This group of neurobehavioral disorders includes several pervasive disorders that remain during a person's whole lifetime, thereby resulting in substantial costs. The group of metabolic-related health effects (obesity, diabetes) also has relatively high cost estimates. This is especially due to a large prevalence of diabetes and obesity within society. The group of immunological diseases, disorders and conditions is not sufficiently quantified to draw conclusions for this purpose, and clearly need further study. Especially considering the increasing incidence in immunological diseases, such as asthma and allergies, and likely contribution of EDCs in disease etiology.

Using this cost-based approach, it can be recommended to give priorities on the development and regulatory inclusion of test guidelines for EDCs that are associated with neurodevelopmental toxicity, diabetes and obesity, as well as to decrease the uncertainty related to immunological disorders. It could be highly valuable, for instance, to evaluate if current information requirements in the various regulatory frameworks sufficiently cover endpoints related to e.g. neurotoxic, metabolic and immune diseases. At present, the common tests used to evaluate the safety of chemicals in the legislative framework (such as the Extended One-Generation Reproductive Toxicity Study, OECD TG-443), does not oblige to test for developmental neurotoxicity endpoints, nor immunological endpoints. This can easily be solved since for developmental neurotoxicity and immunological endpoints, the OECD TG-443 provides relevant cohorts for these endpoints. Yet at present, this is not standard procedure to incorporate these cohorts. In addition, the human relevance of some apical endpoints in animal studies is limited. A more mechanism-based assessment of (new) chemicals, thereby focusing on human-relevant effects, could greatly strengthen current chemical risk assessment processes. An additional merit here would be that these types of studies can very well be performed in human-relevant, *in vitro* assays, without the additional need of animal experiments and potentially even reduce the need of animal tests in chemical risk assessment.

Table 10. An overview on the degree/extent of cost quantification of EDC-associated health effects: EDC-associated socio-economic costs in this and other reports (bright green); literature on costs available: may be subject for future EDC-associated socio-economic cost analysis (medium grey); no or limited literature on costs available (dark grey). Names of health effects clusters/categories that are not assessed are depicted in white.

EDC-Related health effects
1. Reproductive health
Female reproductive problems
Female fecundity and fertility
Reduced female fecundity (lower number of offspring)
Reduced female fertility
Infertility
Adverse pregnancy outcomes
Ectopic pregnancy
Spontaneous abortions (miscarriages)
Hypertensive disorders of pregnancy, incl. pregnancy-induced hypertension and pre-eclampsia
Intrauterine growth restriction (IUGR)
Preterm delivery
Low birth weight or length
Birth defects
Disturbed (decreased) lactation period
Polycystic ovarian syndrome (PCOS)
Endometriosis
Reproductive tract abnormalities
Uterine fibroids
Abnormal vaginal, cervical, uterine, and oviduct anatomy
Ovaries: Premature ovarian failure (POF), decreased ovarian reserve/increased atresia, aneuploidy, granulosa steroidogenesis, altered primordial follicles, follicle growth, oocyte quality
Vaginal adenosis (benign abnormality)
Premature thelarche
Female idiopathic precocious puberty / early menarche
Female delayed puberty
Disturbed menstruation cycle (Oligomenorrhea)
Early age at menopause
Male reproductive problems
Cryptorchidism
Hypospadias
Other male reproductive organ abnormalities (reduced testis weight, abnormal small penis, problems efferent ducts, altered AGD, morphology of seminiferous tubules, nipple retention)
Declining fertility due to reduced semen quality (abnormalities) and quantity (oligospermia)
Testicular dysgenesis syndrome (TDS)
Epididymal cysts (infection/inflammation of the tube that carries semen out of the testicle)
Orchitis (infection/inflammation of testis)
Male delayed puberty
Prostatic intraepithelial hyperplasia (PIN)
Prostatitis (prostate inflammation)
2. Neurodevelopmental syndromes and conditions
Neurobehavioral disorders
Autism spectrum disorders (ASD)
AD(H)D; attention deficit (hyperactivity) disorder
IQ loss
Mental retardation
Cerebral palsy
Neural tube defects
Psychomotor retardation, memory, learning problems
Depressive disorders
Behavioral problems: social, aggression, anxiety, sexual
3. Hormonal cancers
Hormone-related cancers
Breast cancer
Endometrial cancer
Ovarian cancer
Clear cell adenocarcinoma of the vagina and cervix uteri
Prostate cancer
Testis (testicular germ cell) cancer
Thyroid cancer
4. Effects on the metabolic system
Metabolic syndromes
Obesity (child and adult)
Diabetes mellitus (type 2)
Diabetes type 1
Metabolic syndrome
Cardiovascular system
Cardiovascular disease (direct and indirect)
Cardio protection
Hypertension
5. Immune system disorders
Immune function, immune diseases and disorders
Increase of systemic infectious diseases due to altered immune response
Increase of local infections due to altered immune response
Periodontal disease
Otitis media
Respiratory tract infections
Exanthema subitum
Allergies other than asthma: allergic rhinitis, allergic conjunctivitis and atopic dermatitis (eczema)
Autoimmune diseases (incl. thyroid disease)
Autoimmune thyroid disease (AITD) (e.g. Hashimoto's thyroiditis, Graves' disease)
Multiple sclerosis (MS)
Systemic lupus erythematosus (SLE)
Rheumatoid arthritis
Ulcerative colitis
Asthma, childhood asthma, wheeze
Myalgic encephalopathy/chronic fatigue syndrome/post viral fatigue syndrome (ME/CFS/PVFS)
Fibromyalgia (rheumatic disorder)
Hematopoietic disorders and malignancies
Childhood lymphoma
Leukemia
Non-Hodgkin lymphoma
6. Other disorders and conditions
Population effects
Increment death rate among men due to lower testosterone
Sex ratio - declining male population
Neuroendocrine disruption
Various diseases that affect the pituitary or hypothalamus
Adrenal disorders
Adrenocortical hyperplasia (growth, stress response)
Cushing's disease
Thyroid disruption
Adult (sub)hypothyroidism
Congenital hypothyroidism (causing mental retardation)
Thyroid resistance syndrome
Bone disorders
Increased risk of bone fractures
Osteoporosis
Other bone disorders (e.g. orthopedic defects, irregular calcifications)

5.4. Recommendations

Socio-economic cost estimates of EDCs

- Use socio-economic cost estimates to show **the extent of the potential impact** of EDC-related health effects on society;
- Use and further develop the **modular approach** that was introduced in this report to provide context for interpretation of a disease and related costs, endocrine mechanisms and its (potential) link with EDCs. This will provide more structure, transparency, uniformity and completeness of information. The modular approach could also be applied in a broader perspective to analyze other health impacts, a potentially causal agent, and associated socio-economic costs;
- For **transparency**, provide background study parameters of source cost-of-disease studies, as proposed in the modular approach presented in this report (providing a breakdown of costs such as proposed in Table 8). As such, differences and similarities can easily be detected by looking at crucial parameters and type of costs taken into account;
- Develop a **standardized** cost estimate approach for cost-benefit evaluations in the context of hazardous substances. Set criteria what kind of cost should be included and (best applicable) methodology to be used, as a minimum, in order to declare validity of the results;
- Since there is a difference in interpretation in types of costs, it would be preferred to **separate costs** related to direct cost ("real" expenditures) from indirect and intangible costs (cost that place a burden on society or on the quality of lives).

Socio-economic research

- More research is needed towards **costs of EDC-effects that are not yet quantified**;
- It seems valuable to perform European studies on the socio-economic **impact of IQ loss**. At the moment only US studies are available. Furthermore, it would be valuable to further reflect upon the meaning of this loss or value forgone in the context of societies in which average IQ level is increasing;
- More **European-wide cost-of-disease studies** are needed, to avoid uncertainties resulting from extrapolating from one subpopulation or country to another. This will become even more relevant since European policy will become increasingly important.

Research on EDCs

- There is a need to generate more data on the **EDC-attributable factor** to disease burden and individual health effects, as well as the (general) hormonal attribution to diseases;
- More **well-designed epidemiological and toxicological studies** should be performed, e.g. that include sensitive window of exposure to EDCs, such as the developing child;
- Especially for EDC-associated immunological effects, there is a need to generate more data to close the information gap on adverse effects, mechanisms, and contribution of EDCs;
- As **neurodevelopmental disorders and metabolic disorders** appear to have a high socio-economic burden, it is recommended to focus on these health effects in current testing frameworks and develop and/or implement adequate screening methods;
- More efforts are needed that could **bridge the gap** between academic research and regulatory health risk assessment. For example in types of endpoints evaluated, a validated or (in some cases) more uniform study design, relevance of studies, and how results are reported.

Financing and acknowledgements

This report has been financed by the Dutch Ministry of Infrastructure and the Environment (IenM). We thank Julia Verhoeven (RIVM), Betty Hakkert (RIVM), and Ronald Flipphi (IenM) for their support and guidance.

We also would like to thank the reviewers of the draft version of the report and other contributors: Lisette van Vliet (Health and Environment Alliance), Maria Noring and Mattias Carlsson Feng (Swedish Chemicals Agency), Stavros Georgiou (UK Health and Safety Executive), Leonardo Trasande (New York University), Fleur van Broekhuizen, Paul van Gils and ZhiChao Dang (RIVM), Ardine de Wit (RIVM, University Medical Centre Utrecht) and Cees Luttikhuizen (IenM).

The views expressed in this publication reflect the views of the authors and do not necessarily reflect the views of the reviewers and other contributors.

List of Abbreviations

AD(H)D	Attention Deficiency (Hyperactivity) Disorder
AGD	Anogenital distance
AITD	Autoimmune thyroid disease
ART	Assisted reproductive technology
ASD	Autism Spectrum Disorders
BPA	Bisphenol-A
CFS	Chronic fatigue syndrome
DALY	Disability Adjusted Life Year
DAP	dialkyl phosphate
DAP	dialkylphosphate
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DHC	Direct Healthcare Cost
DNHC	Direct Non Healthcare Cost
EAF	environmental attributable fraction
EC	European Commission
ED	Endocrine Disrupting
EDC	Endocrine Disrupting Chemical
EDC-1	The Endocrine Society's Scientific Statement on Endocrine Disrupting Chemicals
EDC-2	The Endocrine Society's Second Scientific Statement on Endocrine Disrupting Chemicals
EEA	European Environmental Agency
EMF	electromagnetic fields
EPA	(US) Environmental Protection Agency
ERR	Exposure response relationship
EU	European Union
GDP	Gross Domestic Product
HEAL	Health and Environment Alliance
IC	Intangible Cost
ICSI	Intracytoplasmatic sperm injection
ID	Intellectual Disability
IHC	Indirect Healthcare Cost
INHC	Indirect Non Healthcare Cost
IPCC	Intergovernmental Panel on Climate Change
IPCS	International Programme on Chemical Safety
IQ	Intelligence Quotient
IRAS	Institute for Risk Assessment Sciences
IUGR	Intrauterine growth restriction
IVF	In vitro fertilization
ME	Myalgic encephalopathy
MS	Multiple Sclerosis
NGO	Nongovernmental Organization
OECD	Organisation for Economic Co-operation and Development
OP	Organophosphate (or: organophosphorous) pesticide
OR	Odds Ratio
PBDE	Polybrominated diphenyl ether
PCB	Polychlorinated biphenyl
PCOS	Polycystic ovarian syndrome

PIN	Prostatic intraepithelial hyperplasia
POF	Premature ovarian failure
POP	Persistent Organic Pollutant
PPP	Purchasing Power Parity
PPPR	Plant Protection Products Regulation
PVFS	Post viral fatigue syndrome
QALY	Quality Adjusted Life Year
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals in the EU
RIVM	(Dutch) National Institute for Public Health and the Environment
SLE	Systemic lupus erythematosus
T	Testosterone
TDS	Testicular dysgenesis syndrome
UNEP	United Nations Environment Programme
UU	Utrecht University
WHO	World Health Organization

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Annex A – References to health effects (potentially) related to EDCs

Health effects (potentially) related to EDC exposure	Source:							
Health effect / class	EDC 1 (2009)	EDC 2 (2015)	EC (2011)	UNEP/WHO (2013)	WHO (2014)	EEA (2012)	other reports	additional references
1. Reproductive health								
Female reproductive problems	x	x						
Female fecundity and fertility	x	x			x			
Reduced female fecundity (lower number of offspring)	x	x	x	x				
Reduced female fertility	x	x	x	x	x			
Infertility	x	x		x	x			
Adverse pregnancy outcomes		x	x	x	x			
Ectopic pregnancy	x				x			
Spontaneous abortions (miscarriages)			x	x	x			
Hypertensive disorders of pregnancy, incl pregnancy-induced hypertension and pre-eclampsia			x		x			
Intrauterine growth restriction (IUGR)				x	x			
Preterm delivery		x	x	x	x			
Low birth weight or length		x	x	x	x			
Birth defects			x					
Disturbed (decreased) lactation period	x							
Polycystic ovarian syndrome (PCOS)	x	x	x	x	x	x		
Endometriosis	x	x	x	x	x	x		
Reproductive tract abnormalities	x	x						
Uterine fibroids	x	x	x	x	x	x		
Abnormal vaginal, cervical, uterine, and oviduct anatomy	x	x						
Ovaries. premature ovarian failure, (POF) decreased ovarian reserve/increased atresia, aneuploidy, granulosa steroidogenesis, altered primordial follicles, decreased follicle growth, oocyte quality	x	x						
Vaginal adenosis (benign abnormality)					x			
Premature thelarche	x				x	x		
Female idiopathic precocious puberty / early menarche	x	x	x	x	x	x		
Female delayed puberty				x		x		
Disturbed menstruation cycle (Oligomenorrhea)		x		x	x			
Early age at menopause		x		x				
Male reproductive problems	x	x	x			x		
Cryptorchidism	x	x	x	x	x	x		
Hypospadias	x	x	x	x	x	x		
Other male reproductive organ abnormalities (reduced testis weight, abnormal small penis, problems efferent ducts, altered AGD, morphology of seminiferous tubules, nipple retention)		x						
Declining fertility due to reduced semen quality (abnormalities) and quantity (oligospermia)	x	x	x	x	x	x		
Testicular dysgenesis syndrome (TDS)		x		x	x	x		
Epididymal cysts (infection/inflammation of the tube that carries semen out of the testicle)		x			x			
Orchitis (infection/inflammation of testis)		x			x			
Male delayed puberty		x		x		x		
Prostatic intraepithelial hyperplasia (PIN)		x				x		
Prostatitis (prostate inflammation)		x		x				
2. Neurological/developmental syndromes and conditions								
Neurobehavioral disorders		x				x		
Autism spectrum disorders		x	x	x	x			
ADD and ADHD; attention deficit (hyperactivity) disorder			x	x	x			
IQ loss		x	x	x		x		
Mental retardation					x			
Cerebral palsy			x					
Neural tube defects			x					
Psychomotor retardation, memory, learning problems		x		x	x			
Depressive disorders					x			
Behavioral problems: social, aggression, anxiety, sexual		x		x				
3. Hormonal cancers								
Hormone-related cancers		x	x					
Breast cancer	x	x	x	x	x	x		
Endometrial cancer		x	x	x	x			
Ovarian cancer		x	x	x	x	x		
Clear cell adenocarcinoma of the vagina and cervix uteri		x			x			
Prostate cancer	x	x	x	x	x	x		
Testis (testicular germ cell) cancer	x	x	x	x	x			
Thyroid cancer			x	x				
4. Effects on the metabolic system								
Metabolic syndromes	x	x	x			x		
Obesity	x	x	x		x	x		
Obesity child							x	Reviewed (Legler et al., 2015)(DDE, BPA)
Obesity adult				x				
Diabetes mellitus (type 2)	x	x	x	x	x			
Diabetes type 1		x		x				
Metabolic syndrome			x	x		x		
Cardiovascular system								
Cardiovascular disease (direct and indirect)	x	x			x			
Cardio protection	x							
Hypertension					x			

Health effects (potentially) related to EDC exposure Health effect / class	Source: EDC-1 (2009)	EDC-2 (2015)	EC (2011)	UNEP/WHO (2013)	WHO (2014)	EEA (2012)	other reports	additional references
5. Immune system disorders								
Immune function, immune diseases and disorders						x		
Increase of systemic infectious diseases due to altered immune response				x				
Increase of local infections due to altered immune response				x				
Periodontal disease				x				
Otitis media							x	(Buscail et al., 2015; Weisglas-Kuperus, Vreugdenhil, & Mulder, 2004b) (OPs, PCBs)
Respiratory tract infections							x	(Granum et al., 2013; Stølevik et al., 2011) (PFCs, PCBs, dioxins)
Exanthema subitum							x	(Stølevik et al., 2011)(PCBs, dioxins)
Allergies other than asthma: allergic rhinitis, allergic conjunctivitis and atopic dermatitis (eczema)								
Autoimmune diseases				x		x		
Autoimmune thyroid disease (AITD) (e.g. Hashimoto's thyroiditis, idiopathic myxedema, asymptomatic thyroiditis, endocrine exophthalmus, and Graves' disease)	x			x	x	x		
Multiple sclerosis (MS)			x					
Systemic lupus erythematosus (SLE)								reviewed (Mokarizadeh, Faryabi, Rezvanfar, & Abdollahi, 2015) (OCs, herbicides)
Rheumatoid arthritis								reviewed (Mokarizadeh et al., 2015) (insecticides)
Ulcerative colitis							x	(Steenland, Zhao, Winquist, & Parks, 2013)(PFOA)
Asthma, childhood asthma, wheeze			x	x			x	(Midoro-Horiuti et al., 2010; Stølevik et al., 2011; Weisglas-Kuperus et al., 2004b) (BPA, PCBs, dioxins)
Myalgic encephalopathy/chronic fatigue syndrome/post viral fatigue syndrome (ME/CFS/PVFS)			x					
Fibromyalgia (rheumatic disorder)			x					
Hematopoietic disorders and malignancies								
Childhood lymphoma				x				
Leukemia				x				
Non-Hodgkin lymphoma				x				
6. Other disorders and conditions								
Decrease population								
Increment death rate among men due to lower testosterone							x	reviewed (Hauser et al., 2015) (phthalates)
Sex ratio - declining male population			x	x	x			
Neuroendocrine disruption	x	x						
Various diseases that affect the pituitary or hypothalamus	x	x						
Adrenal disorders		x				x		
Adrenocortical hyperplasia (growth, stress response)				x				
Cushing's disease				x				
Thyroid disruption		x				x		
Adult (sub)hypothyroidism	x			x	x	x		
Congenital hypothyroidism (causing mental retardation)				x	x			
Thyroid resistance syndrome	x							
Bone disorders				x				
Increased risk of bone fractures				x				
Osteoporosis				x				
Other bone disorders (e.g. orthopedic defects, irregular calcifications)				x				

Annex B – Detailed evaluation of parameters relating to EDC-attributable cost per disease

Specification of EDC-related cost of health effects in EU28

	Scope / Substance			Original cost of disease study / general parameters									Specification of costs										Total cost		Additional adjustment by EDC-cost study			Incidence or Prevalence				Total EU28 EDC cost
Disease, disorder or condition	Scope	Substance	Reference	Study author	Year of publication	Year	Country	Cost per person/patient/unit	Study perspective	Currency / currency year	Time horizon	Discounting	Direct Healthcare Cost (DHC)	DHC specification	Direct Non Healthcare Cost (DNHC)	DNHC approach	Indirect Healthcare Cost (IHC)	IHC approach	Indirect Non Healthcare Cost (INHC)	INHC approach	Intangible costs (IC)	IC approach	Total Cost	Sensitivity Analysis	Approach / adjustment or extrapolation	Total cost, adjusted	Total cost, adjusted and increased	Relative incidence or prevalence (%)	Absolute incidence or prevalence (#)	% of cases attributable to EDC	Amount of cases attributable to EDC in EU28	Total EDC attributable cost for the endpoint in EU28 (billion €)
Reproductive tract and fertility																																
1. Fertility																																
Nordic Council report	male fertility	n/a	n/a	Nordic Council	2014	2012	EU28	person	weighted average cost per infertile man	€ / 2013	lifetime cost	4%	€ 2 738	[illegible]	not included	n/a	not included	n/a	€ 760	lost working hours per couple	not included	n/a	[illegible]	n/a	n/a	n/a		[illegible]	[illegible]	2%, 20%, 40%	[illegible]	[illegible]
HEAL report	male & female fertility	n/a	n/a	[illegible]	[illegible]	1992-1998	Sweden	per treatment/live birth	mean cost per treatment	$ / 1998	treatment period	0%	$ 1170	ART treatment (IVF/Embryo Transfer)	not included	n/a	$ 713	[illegible]	not included	n/a	not included	n/a	[illegible]	n/a	not included	[illegible]		[illegible]	[illegible]	2%, 5%	[illegible]	[illegible]
Trasande report	male fertility	[illegible]	[illegible]	Christiansen	[illegible]	2000-2010	Denmark	couple	weighted average cost per couple	€ / 2013	[illegible]	3%	€ 6 607	[illegible]	not included	n/a	not included	n/a	not included	n/a	not included	n/a	€ 6 607	n/a	[illegible]	€ 7 [illegible] / couple		not specified	not specified	[illegible]	[illegible]	4,71
2. Cryptorchidism																																
Nordic Council report	n/a	n/a	n/a	Nordic Council	2014	2012	EU28	person	infant treatment	€ / 2013	lifetime cost	DHC: 0%, NHC: 0%, IC: 1,5%	€ 4 429	surgery and care based on Swedish patient registry	not included	n/a	not included	n/a	€ 1.000	lost working hours parents	[illegible]	[illegible]	[illegible] / infant	n/a	n/a	n/a		[illegible]	[illegible]	2%, 20% or 40%	[illegible]	[illegible]
HEAL report	n/a	n/a	n/a	[illegible]	2009	2003-2007	US	person	[illegible]	$ / 2009	lifetime cost	[illegible]	[illegible]	[illegible]	not included	n/a	not included	n/a	not included	n/a	not included	n/a	[illegible]	not shown	n/a	n/a		[illegible]	[illegible]	2%, 5%	[illegible]	[illegible]
Trasande report	n/a	[illegible]	[illegible]	Nordic Council	2014	2012	EU28	person	infant treatment	€ / 2013	lifetime cost	DHC: 0%, NHC: 0%, IC: 1,5%	€ 4 429	surgery and care	not included	n/a	not included	n/a	[illegible]	lost working hours parents	[illegible]	[illegible]	[illegible] / infant	n/a	[illegible]	[illegible]		[illegible]	[illegible]	not specified [illegible]	[illegible]	[illegible]
3. Hypospadias																																
Nordic Council report	n/a	n/a	n/a	Nordic Council	2014	2012	EU28	person	infant treatment	€ / 2013	lifetime cost	DHC: 0%, NHC: 0%, IC: 1,5%	[illegible]	surgery and care based on Swedish patient registry [illegible]	not included	n/a	not included	n/a	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] / infant	n/a	n/a	n/a		[illegible]	[illegible]	2%, 20% or 40%	[illegible]	[illegible]
Neurodevelopmental diseases and disorders																																
4. Autism / Autism Spectrum Disorders (ASD)																																
HEAL report	n/a	n/a	n/a	Knapp	2009	[illegible]	UK	person	children and adults with and without intellectual Disability [illegible]	[illegible]	[illegible]	0%	[illegible]	Accommodation or residential care, respite care, hospital services, other health and social services, treatment	not included	n/a	not included	n/a	[illegible]	[illegible]	not included	n/a	[illegible]	n/a	[illegible]	[illegible]		[illegible]	not specified	[illegible]	not specified	[illegible]
Trasande report	n/a	[illegible]	[illegible]	[illegible]	2014	[illegible]	UK	person	children and adults with and without intellectual Disability [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Accommodation or residential care, respite care, medical and non-medical services	not included	n/a	not included	n/a	[illegible]	[illegible]	not included	n/a	[illegible]		[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
5. Attention Deficit Hyperactivity Disorder (ADHD)																																
HEAL report	n/a	n/a	n/a	Schlander	2007	[illegible]	UK, Germany	total drug expenditures	[illegible]	[illegible]	year	0%	€ 78 million	[illegible]	not included	n/a	not included	n/a	not included	n/a	not included	n/a	€ 78 million	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	2%, 5%	[illegible]	[illegible]
Trasande report	n/a	[illegible]	[illegible]	[illegible]	2014	[illegible]	Netherlands	person	n/a	[illegible]	year	0%	[illegible]	[illegible]	not included	n/a	not included	n/a	[illegible]	[illegible]	not included	n/a	[illegible] per person	n/a	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Trasande report	n/a	[illegible]	[illegible]	[illegible]	2014	[illegible]	Netherlands	person	n/a	[illegible]	year	0%	[illegible]	[illegible]	not included	n/a	not included	n/a	[illegible]	[illegible]	not included	n/a	[illegible] per person	n/a	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
6. IQ loss																																
Trasande report	n/a	[illegible]	[illegible]	[illegible]	2014	[illegible]	[illegible]	IQ point	n/a	[illegible]	[illegible]	[illegible]	not included	n/a	not included	n/a	not included	n/a	[illegible]	[illegible]	not included	n/a	[illegible]	n/a	[illegible]	[illegible]		n/a	n/a	[illegible]	[illegible]	[illegible]
Trasande report	n/a	[illegible]	[illegible]	[illegible]	2014	[illegible]	US	IQ point	n/a	[illegible]	[illegible]	[illegible]	not included	[illegible]	not included	n/a	not included	n/a	[illegible]	[illegible]	not included	[illegible]	[illegible]	n/a	[illegible]	[illegible]		n/a	n/a	[illegible]	[illegible]	[illegible]
7. Mental retardation																																
Trasande report	n/a	[illegible]	[illegible]	Gustavsson	2011	2010	[illegible]	person	weighted average by age and prevalence in each country	€ / 2010	year	0%	[illegible]	[illegible]	[illegible]	[illegible]	not included	[illegible]	not included	n/a	not included	n/a	[illegible] / year	n/a	[illegible]	[illegible]		1%	[illegible]	not specified	[illegible]	[illegible]
Trasande report	n/a	[illegible]	[illegible]	Gustavsson	2011	[illegible]	[illegible]	[illegible]	weighted average by age and prevalence in each country	[illegible]	year	0%	[illegible]	[illegible]	[illegible]	[illegible]	not included	n/a	not included	n/a	not included	n/a	[illegible] / year	n/a	[illegible]	[illegible]		1%	[illegible]	not specified	[illegible]	[illegible]

Specification of EDC-related cost of health effects in EU28

Disease, disorder or condition	Scope	Substance	Reference	First author	Year of publication	Year	Country	Cost per person/societal cost	Study perspective	Currency / currency year	Time horizon	Discounting	Direct Healthcare Cost (DHC)	DHC specification	Direct Non-Healthcare Cost (DNHC)	DNHC approach	Indirect Healthcare Cost (IHC)	IHC approach	Indirect Non-Healthcare Cost (INHC)	INHC approach	Intangible costs (IC)	IC approach	Total Cost	Sensitivity Analysis	Approach / adjustment or extrapolation	Total cost, adjusted	Total cost, adjusted and summed	Relative incidence or prevalence EU	Absolute incidence or prevalence EU	% of cases attributable to EDC	Amount of cases attributable to EDC in EU28	Total EDC attributable cost for the endpoint in EU28 (billion €)
I. Hormonal cancers 1. Breast cancer																																
HEAL report	n/a	n/a	n/a	Luengo-Fernandez	2013	2009	EU27	societal cost	n/a	€ / 2009	1 year	productivity loss by 3.5%	€ 6 735 billion	Primary care (€ 325 million), Outpatient care (€ 426 million), Accident and emergency care (€ 66 million), Inpatient care (€ 2 541 million), Medications (€ 3 [illegible] million)	not included	n/a	not included	n/a	€ 8.246 billion	Productivity losses attributable to mortality (€3.25 billion), Productivity loss by informal care (€ 1.20 billion), Productivity loss attributable to morbidity (€ 1.79 billion)	not included	n/a	€ 14 971 billion	n/a	from EU27 to EU28 estimate (+Croatia), adjusted to 2012	€ 16 billion / total societal cost EU28		90 / 100 000 incidence	not reported (would be 0.09%*505.7 million=455 000)	2% 5%	not reported (would be [illegible] (2%), 22 750 (5%))	0.30 (2%) 0.8 (5%)
2. Prostate cancer																																
HEAL report	n/a	n/a	n/a	Luengo-Fernandez	2013	2009	EU27	societal cost	n/a	€ / 2009	1 year	productivity loss by 3.5%	€ 5 433 billion	Primary care (€ 181 million), Outpatient care (€ 332 million), Accident and emergency care (€ 32 million), Inpatient care (€ 1 762 million), Medications (€ [illegible] million)	not included	n/a	not included	n/a	€ 2 [illegible] billion	Productivity losses attributable to mortality (€ 752 million), Productivity loss attributable to morbidity (€ 596 million), Productivity loss informal care (€ 1875 million)	not included	n/a	€ 8.[illegible] billion	n/a	from EU27 to EU28 estimate (+Croatia) adjusted to 2012	€ [illegible] billion / total societal cost EU28		62 / 100 000 incidence	not reported (would be 0.062%*505.7 million=315 500)	2% 5%	not reported (would be 6 170 (2%), 15 400 (5%))	0.19 (2%) 0.46 (5%)
3. Testicular cancer																																
Nordic Council report	n/a	n/a	n/a	Nordic Council	2014	2012	EU28	person	n/a	€ / 2012	lifetime cost	direct and indirect cost by 4%, intangible cost 1.5%	€ 2 340 / person	surgery and care	not included	n/a	not included	n/a	€ 1 [illegible] / person	Productivity loss, based upon various scenarios	€ 76 [illegible] / person	QALY: Undiscounted loss 1.86, discounted loss 1.09; 1 QALY= € 75 [illegible]	€ 80 [illegible]	n/a	n/a	n/a		6.1 / 100 000 (Larsen Research UK 2014)	[illegible]	2% 20% 40%	[illegible] (2%), [illegible] (20%), [illegible] (40%)	0.025 (2%), 0.249 (20%), 0.499 (40%)
Trasande report	n/a	PBDE (PBDE-47, PBDE-99, PBDE-153) in maternal samples	Hardell et al. 2006	Nordic Council	2014	2012	EU28	person	n/a	€ / 2012	lifetime cost	direct and indirect cost by 4%, intangible cost 1.5%	€ 2 340 / person	surgery and care	not included	n/a	not included	n/a	€ 1 [illegible] / person	Productivity loss, based upon various scenarios	€ 76 [illegible] / person	QALY: Undiscounted loss 1.86, discounted loss 1.09; 1 QALY= € 75 [illegible]	€ 80 [illegible]	n/a	Adjusted for per capita GDP PPP in Sweden. Adjusted to 2012 and medical cost inflation	€ 134 [illegible]		7.1 / 100 000 (GLOBOCAN 2012)	[illegible]	[illegible] (low), [illegible] (base case)	[illegible] (low), [illegible] (base case)	0.312 (low), [illegible] (base case)
II. Metabolic syndrome 11. Obesity																																
HEAL report	children and adults	n/a	n/a	European Commission	2007	2006	EU25	societal cost	"average" obese person	€ / 2006 GDP	1 year	0%	not specified	obesity related primary medical consultation, hospital treatment and medicines	not included	n/a	not included	n/a	not specified	productivity loss from obesity related mortality and morbidity	not included	n/a	€ [illegible] billion / total EU	n/a	n/a	n/a		overweight 30%, Obesity 20% men 23% women	[illegible] million (overweight + obese)	2% 5%	4 million (2%), 10 million (5%)	1.63 (2%), 4.08 (5%)
Trasande report	children	DDE (p,p'-DDE in cord serum)	[illegible] et al. 2015	Finkelstein et al. 2014	2014	various	US	person	increment of healthcare related cost of an obese child compared to normal child	$ / 2012	lifetime	3%	$ 19200	Medical expenditures, depending on reviewed study	not included	n/a	not included	n/a	not included	n/a	not included	n/a	$ 19200 / person	n/a	converted to 2010 using the general US Consumer Price Index. Adjusted for PPP GDP to that of the United States. Conversion international dollars to €	€ 12 [illegible] / capita		not specified	not specified ([illegible] 10 year olds)	0.26 % (base case), [illegible] % (high)	1555 (base case), 1461 (high)	0.0246 (base case), [illegible] (high)
Trasande report	children	BPA (creatinine-adjusted BPA in maternal urine)	Valvi et al. 2013	Finkelstein et al. 2014	2014	various	US	person	increment of healthcare related cost of an obese child compared to normal child	$ / 2012	lifetime	3%	$ 19200	Medical expenditures, depending on reviewed study	not included	n/a	not included	n/a	not included	n/a	not included	n/a	$ 19200 / person	n/a	similar to the adjustment in cost estimate for DDE related childhood obesity. In addition, to estimate lifetime costs of obesity at age 4 data inputs from the primary studies were updated: indirect healthcare cost (DALY%) were added, accounting for different timing and applying 3% discounting	€ 46 [illegible] / capita	€ 66 [illegible] / capita	not specified	not specified	increments in prevalence between 0.09% and 2.9%	42 [illegible] additional cases of childhood obesity, 31 [illegible] additional cases of adult obesity	1.54
				Trasande	2012		US	person	study not found				not included	n/a	not included	n/a		DALY								€ 17 [illegible] / capita						
Trasande report	adults	Phthalates [illegible] in urine	[illegible] et al. 2014	[illegible]	2012	[illegible]	US	person	overweight and obese adults	$ / [illegible]	year	3%	$ 2741	annual medical expenditures	not included	n/a	not included	n/a	not included	n/a	not included	n/a	$ 2741 / person / year	n/a	Aggregated 12 years of health care expenditures beginning ten years later, using 3% discounting. Converted to $ 2010, multiplied by the ratio of each country's PPP adjusted per capita GDP to that of the US	€ [illegible] / capita / lifetime	€ [illegible] / capita	not specified	not specified	not specified	[illegible] attributable cases of obese females	15.6
				[illegible]	2006	[illegible]	US	person	overweight and obese adults	$ / [illegible]	lifetime	3%	not included	n/a	not included	n/a	not included	n/a	not included	n/a	$ [illegible]	QALY loss [illegible] QALY per adult, valued at $ [illegible] per QALY	$ [illegible]	results not shown (QALY value $ [illegible] and discounting 0-5%)	18 years of discounting at 3%, multiplied by the ratio of each country's PPP adjusted per capita GDP to that of the US	€ [illegible] / capita						
12. Diabetes type 2																																
HEAL report	adults	n/a	n/a	[illegible]	2012	various years depending on original study per country	EU (Spain, UK, Germany, France and Italy)	society	diabetes type 1 and 2	€ / 2010	year	3%	€ [illegible] billion	Medical costs, some of which may not necessarily caused by diabetes, but can be exacerbated by it: inpatient care, treatment of diabetes related complications. Outpatient care. Medication: insulin and oral anti-diabetic medication, non-diabetes drugs	not included	n/a	not included	n/a	€ 98.4 billion	included absenteeism, early retirement, social benefits; Not included productivity losses (presenteeism), the cost of premature mortality and any care costs associated with caring for a diabetic relative	not included	n/a	€ 188 billion	n/a	EU5 comprises 62.5% of EU28 (...) updated based on population [illegible] EU28 cost estimate	€ [illegible] billion		6% of EU population between ages 20-79	30 million	2% 5%	600 000 (2%), 1.5 million (5%)	6 (2%), 15 (5%)
Trasande report	adults	DDE [illegible]	Wu et al. 2013 (base case), Turyk et al. 2009 (high)	Zhang	2010	various years depending on original study per country	worldwide	person	diabetes type 1 and 2	international $ / 2010	year	3%	$ 1527 / year	total healthcare cost expenditures, but criteria is different per country of study	not included	n/a	not included	n/a	not included	n/a	not included	n/a	$ 1527 / year	n/a	Given that newly incident diabetes results in costs over multiple years of each subsequent lifetime, annual costs were aggregated over a fifteen-year period, using 3% discounting	€ 25 [illegible]		not specified	not specified	not specified, calculated using EU prevalence of 30 million: 0.09% - 1.9%	28 200 (base case), [illegible] (high)	0.835 (base case), 16.6 (high)
Trasande report	adults	Phthalates (total phthalate metabolites in urine)	Sun et al. 2014	Zhang	2010	various years depending on original study per country	worldwide	person	diabetes type 1 and 2	international $ / 2010	year	3%	$ 1527 / year	total healthcare cost expenditures, but criteria is different per country of study	not included	n/a	not included	n/a	not included	n/a	not included	n/a	$ 1527 / year	n/a	Given that newly incident diabetes results in costs over multiple years of each subsequent lifetime, annual costs were aggregated over a fifteen-year period, using 3% discounting	€ 25 [illegible]		not specified	not specified	not specified, calculated using EU prevalence of 30 million: 0.07%	20 [illegible]	0.607
13. Increased death rate due to reduced testosterone																																
Trasande report	adult men 55-64 years	Phthalates (metabolites of di-2-ethylhexyl phthalate and dibutyl phthalate) in urine of men (40-60 years) as related to decreased T testosterone	Phthalate and decreased T: Meeker and Ferguson 2014; lower T and mortality: Araujo et al. 2011	Max (unpublished result cited in Trasande et al. [illegible])	2012	2009	US	person	unknown	$ / 2009	lifetime	unknown	not included	n/a	not included	n/a	not included	n/a	not specified	Lifetime economic productivity loss due to death, among 55-59 and 60-64 year olds from US sources in 2009 dollars	not included	n/a	not specified	n/a	updated to 2010 Euros using the ratio of purchasing power parity per capita GDP of each country to the US, the Euro/dollar exchange rate (1.33) and trends in general consumer prices from the US	€ [illegible]		not specified	241 167	not specified (calculated 10.1%)	24 [illegible]	7.[illegible]



ISBN: 978-90-393-6538-0

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